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Cancer Incidence and Risk of Multiple Cancers after Environmental Asbestos Exposure in Childhood—A Long-Term Register-Based Cohort Study

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Abstract: Objectives: To examine the asbestos-associated cancer incidence and the risk of multiple cancers in former school children exposed to environmental asbestos in childhood. Methods: A cohort of 12,111 former school children, born 1940–1970, was established using 7th grade school records from four schools located at a distance of 100–750 m in the prevailing wind direction from a large asbestos-cement plant that operated from 1928 to 1984 in Aalborg, Denmark. Using the unique Danish personal identification number, we linked information on employments, relatives' employments, date of cancer diagnosis, and type of cancer and vital status to data on cohortees extracted from the Supplementary Pension Fund Register (employment history), the Danish Cancer Registry, and the Danish Civil Registration System. We calculated standardized incidence rates (SIRs) for asbestos-associated cancers, all cancers, and multiple cancers using rates for a gender and five-year frequency-matched reference cohort. Results: The overall incidence of cancer was modestly increased for the school cohort (SIR 1.07, 95% confidence interval (CI) 1.02–1.12) compared with the reference cohort. This excess was driven primarily by a significantly increased SIR for malignant mesothelioma (SIR 8.77, 95% CI 6.38–12.05). Former school children who had combined childhood environmental and subsequent occupational exposure to asbestos had a significantly increased risk of lung cancer. Within this group, those with additional household exposure by a relative had a significantly increased SIR for cancer of the pharynx (SIR 4.24, 95% CI 1.59–11.29). We found no significant difference in the number of subjects diagnosed with multiple cancers between the two cohorts. Conclusions: Our study confirms the strong association between environmental asbestos exposure and malignant mesothelioma and suggests that environmental asbestos exposure in childhood may increase the overall cancer risk later in life.

Keywords: cancer; asbestos; registry study; mesothelioma; pharynx cancer; environmental exposure; childhood

1. Introduction

Health risks associated with asbestos exposure, including the risk of certain cancers, have been known for many years, but research has been devoted mainly to occupational

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asbestos exposure or exposure in adults in general, and rarely to asbestos exposure in childhood [1]. Asbestos continues to be used around the world. This poses a risk not only for those working with asbestos, but also for the general population, including children who are exposed to environmental asbestos [2–7]. The International Agency for Research on Cancer (IARC) has concluded that all forms of asbestos may cause mesothelioma and cancer of the lung, larynx, and ovary [8]. Furthermore, the IARC has found a positive association between asbestos exposure and cancer of the pharynx, stomach, colon, and rectum, though the epidemiological evidence for these cancers is limited. The primary routes of exposure to asbestos are inhalation and ingestion [8].

We have studied environmental asbestos exposure both in adults and children and found a significantly increased risk for mesothelioma development [9,10]. We also found some evidence for an increased risk of haematological cancers in children exposed to asbestos [11]. Only a few studies [12,13] have investigated to which extent prior asbestos exposure contributes to the increasing incidence of multiple primary cancers, seen in recent decades with the advent of better diagnostic techniques, increasing longevity, and improved survival in cancer patients [14]. One study proposed that a gene/environment interaction involving BAP1, environmental exposure to asbestos, and UV irradiation played a role in a family with a high incidence of multiple primary cancers [13]. In another study, five patients with multiple primary tumors were found to have had a history of occupational asbestos exposure [12].

Denmark had one factory which was a producer of asbestos-containing products, until an asbestos ban was introduced in the 1980s. The Danish asbestos cement plant (Dansk Eternit Fabrik A/S) was located in Aalborg city in Northern Denmark, where production of asbestos cement products took place from 1928 until 1988. A total of approximately 620,000 tons of asbestos (89% chrysotile) was consumed during the production period [15].

The cancer incidence among the workers at the asbestos plant in Aalborg has been examined in previous cohort studies [16]. Raffn et al. found a significantly increased overall incidence (SIR = 1.22, 95% CI 1.12–1.32) of cancer among men employed at this plant compared with all Danish men in the period between 1928 and 1984 [16]. Significant excess risks for cancer among the male workers were found for cancer of the lung, pleura, mediastinum, stomach, penis, and larynx for the group of asbestos cement workers employed between the years 1928 to 1940, with 15 years of latency [16].

The aim of the present study was to examine the risk of all types of cancer, including asbestos-associated cancers and multiple cancers in the same subject, in a cohort of former school children who were exposed to environmental asbestos from the asbestos cement plant in their neighborhood

2. Materials and Methods

2.1. Population

School children from four primary schools located in the prevailing wind direction at a distance of 100–750 m from the asbestos cement plant near the center of Aalborg city were selected for the study [17]. From the Aalborg City Archives, we retrieved 17,838 seventh grade school records from the four schools on all former pupils born between 1940 and 1970. These pupils were identified through their unique 10-digit personal identification number (CPR number). A CPR number has been assigned to all residents in Denmark by the Danish Civil Registration System (CRS) since 2 April 1968 [18]. Examination of the school records led to exclusion of some pupils due to lack of unique identification (n = 1214), invalid CPR number (n = 139), birth year either before 1940 or after 1970 (n = 1649), and multiple records (n = 2723). Multiple records occurred because some pupils had attended more than one of the four schools. A reference cohort, frequency matched 1:9 on sex and five-year age intervals, was sampled from the CRS. Furthermore, we excluded subjects who had emigrated (nReference = 6), died (nReference = 1), or been diagnosed with cancer (nSchool = 2, nReference = 32) before start of school in the year of their twelfth-year birthday.

2.2. Asbestos Exposure

School cohortees were, per definition, environmentally exposed, not only by attending the schools near the factory, but they also lived in the same neighborhood because Danish children were normally assigned to the school nearest to their place of residence. Measurements of asbestos exposure at the asbestos plant in 1948 performed by the Danish National Institute of Occupational Health indicate that asbestos fiber levels may have been 100–1600 times above the present Danish threshold limit value of 0.5 fiber/mL (9). Asbestos production was relatively low-tech, so we assume that there was some asbestos pollution spilled from the plant to its neighborhood. Furthermore, until 1972, asbestos was transported from the port to the plant in hessian bags, allowing leaks and spills [16]. The reference cohort had no known environmental asbestos exposure.

In order to reconstruct potential additional occupational asbestos exposure, we obtained employment history based on individual records from the Danish Supplementary Pension Fund Register (ATP). The ATP has been registering all wage earners aged 16–66 years, working at least 9 h/week, since 1 April 1964, and the register includes company information and date of start and end of each employment. Furthermore, we obtained information from Statistics Denmark on the classification of companies in which cohortees had been employed. Companies were classified according to a five-digit extended version (DSE77) of the International Standard Industrial Classification of all Economic Activities (ISIC) [19]. To assess occupational asbestos exposure, we used DANJEM based on the Nordic Occupational Cancer Study (NOCCA) job-exposure matrix (JEM) [20]. We have edited the JEM to make it compatible with Danish industry codes (DSE77) and supplemented the JEM with data on specific companies with a known historical use of asbestos. The DANJEM characterizes asbestos exposure by estimates of the prevalence and level of exposure in four periods from 1945 until 1994 [20]. Previously, it has been estimated that in the period until the Danish asbestos ban, approximately 150,000 persons were exposed to occupational asbestos, corresponding to approximately 10% of the working population [21]. We classified a cohortee as ever having been exposed to occupational asbestos if the exposure prevalence in the JEM exceeded 50% in at least one job held in the period from April 1964 until 31 December 1994. By this categorisation, 10.0% of the reference cohort were exposed to occupational asbestos exposure. A subject was grouped as exposed from relatives (household exposure) if a relative was assessed as being exposed to occupational asbestos in this period. Relatives, i.e., spouse, mother, father, siblings, and children under 18 years of age, were identified in the CRS by their CPR number. Their individual employment histories, backdating to 1964, were extracted from the ATP. The index subject's mother and father were defined as ever exposed to occupational asbestos if exposure took place in the period from when the index subject was born (at the earliest, April 1964) to his or her 18th birthday. Spouses and children of the index person were defined as ever exposed to occupational asbestos if the index subject was 18+ years old and under 18 years old, respectively. An individual from the school cohort was defined as being exposed to environmental asbestos in the absence of their own occupational asbestos exposure and household asbestos exposure. The reference cohort does not have a known asbestos exposure besides the occupational and household asbestos exposures.

2.3. Cancer

All cancers diagnosed in Denmark have been registered in the Danish Cancer Registry since 1943. The Danish Cancer Registry has a high degree of completeness and accuracy [22]. By linking the CPR number to the Danish Cancer Registry, data on cancer type and date of diagnosis were retrieved for both the school cohort and the reference cohort. The asbestos cancer diseases in our study were selected on the basis of the IARC's classification of cancer sites associated with asbestos exposure, including mesothelioma and cancer of the lung, stomach, colon, rectum, larynx and pharynx, and ovaries [8]. The diagnoses were classified according to extended Danish versions of the International Classification of Diseases version ICD-7 (1943–1977), ICD-O (1978–2003), and ICD-10 (2004 and onwards) [22]. Follow-up

for cancer began 2 April 1968 (start date for CRS) or 1 August the year the subjects turned 12 years old (seventh grade school start) if born after 2 April 1968. It ended on the date of death, emigration, disappearance, or 31 December 2015, whichever came first.

2.4. Tobacco Smoking

Smoking data were available only for some of the lung cancer cases in the Danish Lung Cancer Registry (DLCR), from which we retrieved dichotomized smoking data (ever/never smoker). The DLCR contains information about characteristics in lung cancer patients registered since the year 2000; since November 2013, patient reported outcome measures have been included, as well [23].

2.5. Statistics

The chi-square test was used to compare categorical variables between the two groups of the study population. Age medians were analysed using the Wilcoxon–Mann–Whitney test. Person-years at risk for each subject were calculated according to the follow-up period and split into five-year age and calendar time intervals. SIRs with corresponding 95% confidence intervals (95% CIs) were estimated as the ratio between the observed number of cancers in the school cohort and the expected number of cancers in the reference cohort. In order to estimate the risk significance of the various asbestos exposures, the cohorts were stratified into "environmental asbestos exposure", "household asbestos exposure", "occupational asbestos exposure", and "occupational and household asbestos exposure". Statistical analyses were performed using Stata 15.1 (Stata Corp LLC, College Station, TX, USA).

The study was performed in accordance with the Helsinki Declaration and approved by the Danish Data Protection Agency (j. no.: 2016-41-4787).

3. Results

The final school cohort consisted of 12,111 children who attended one of the four schools nearby the asbestos cement plant (50.3% males and 49.7% females), contributing 592,986 person-years at risk. Table 1 presents the characteristics of the school children and the reference group. The median attained age at the end of follow-up was 62.5 years in the school cohort, with the fewest (3.7%) born in the latest birth period from 1965 to 1970. Significantly more subjects in the school cohort had been occupationally asbestos exposed compared to the reference cohort (16.9% versus 10.0%).

Table 1. Characteristics of the Aalborg School Children Cohort and the sex and age-matched reference cohort.

	School Cohort (*n* = 12,111)		**Reference Cohort (*n* = 108,987)**		
Characteristics	*n*	(%/range)	*n*	(%/range)	*p*-value
Sex					
Male	6087	(50.3)	54,787	(50.3)	
Female	6024	(49.7)	54,200	(49.7)	
Birth-year					
1940–1944	2409	(19.9)	21,687	(19.9)	
1945–1949	2961	(24.5)	26,645	(24.5)	
1950–1954	2671	(22.1)	24,029	(22.1)	
1955–1959	2166	(17.9)	19,498	(17.9)	
1960–1964	1451	(12.0)	13,047	(12.0)	
1965–1970	453	(3.7)	4081	(3.7)	
Person-years of follow-up	592,986		5,131,278		
Median age at analysis	62.5	(13.5–76.0)	62.2	(12.0–76.0)	0.001
Type of asbestos exposure					0.000
Only environmental asbestos exposure/No known asbestos exposure	8013	(66.2)	83,525	(76.6)	
Occupational asbestos exposure	1761	(14.5)	9685	(8.9)	
Household and occupational asbestos exposure	1916	(15.8)	10,398	(9.5)	
Occupational and household occupational asbestos exposure	287	(2.4)	1203	(1.1)	
No Supplementary Pension Fund Register data	134	(1.1)	4176	(3.8)	

3.1. Cancer Incidence Ratios

Table 2 presents the SIRs for the school cohort and the reference cohort. After exclusion of non-melanoma skin cancers, 1827 individuals in the school cohort were registered with at least one primary cancer, 38 of which were malignant mesothelioma. The SIR for malignant mesothelioma was the highest of all the asbestos-associated cancers (SIR 8.77, 95% CI 6.38–12.05). We found a significantly increased incidence both in the group of all cancer types (SIR 1.07, 95% CI 1.02–1.12) and in the group of all asbestos-associated cancers (SIR 1.14, 95% CI 1.05–1.24) compared with the reference cohort. In a sub-analysis excluding malignant mesothelioma cases, the overall cancer incidence ratio was marginally, but significantly, increased (SIR 1.05, 95% CI 1.00–1.10). However, the SIR for all asbestos-associated cancers did not reach significance when malignant mesothelioma was excluded (SIR 1.07, 95% CI 0.99–1.17). Besides malignant mesothelioma, no other asbestos-associated cancer type was significantly elevated, even though an excess risk of cancer of the colon, larynx, lung, pharynx, and stomach was observed. The incidence of ovarian cancer was significantly lower. In total, 155 individuals (1.28%) in the school cohort and 1263 individuals (1.16%) in the reference cohort were diagnosed with more than one cancer. For those with an asbestos-associated cancer as their first primary cancer, 60 persons (10.8%) from the school cohort had more than one cancer (maximum of two cancers), versus 554 persons (12.8%) in the reference cohort (maximum of four cancers).

Table 2. Standardized incidence ratios for cancer (1968–2015) among 12111 former school children from Aalborg.

	All School Children		
Cancer Site	**O/E**	**SIR**	**(95% CI)**
All cancers (minus non-melanoma skin cancers) *	1827/1706.82	**1.07**	**(1.02–1.12)**
All asbestos-associated cancers *	580/509.35	**1.14**	**(1.05–1.24)**
Mesothelioma	38/4.33	**8.77**	**(6.38–12.05)**
Lung	236/213.50	1.11	(0.97–1.26)
Larynx	25/17.26	1.45	(0.98–2.14)
Ovary, fallopian tube and broad ligament	33/46.73	**0.71**	**(0.50–0.99)**
Pharynx	40/30.43	1.31	(0.96–1.79)
Stomach	33/28.56	1.16	(0.82–1.63)
Colon incl. rectosigmoideum	119/112.41	1.06	(0.88–1.27)
Rectum	67/69.29	0.96	(0.75–1.21)
Multiple cancers (>1 cancer)	155/143.74	1.08	(0.92–1.26)

* Individuals with at least one cancer; Bold denotes statistically significant results, $p < 0.05$; Abbreviations: CI, confidence interval; E, expected number of cases; O, observed number of cases, SIR, standardized incidence ratio.

3.2. Cancer Incidence Rates Related to Type of Exposure

All school cohortees were assumed to have been exposed to environmental asbestos. An analysis was performed dividing the cohort into subgroups according to possible additional asbestos exposure in various combinations (household, occupational, and both occupational and household) (Table 3). When the cohort was divided into additional asbestos exposure subgroups, the SIR for all cancers was only significantly increased in the subgroup of school children who were exposed to both environmental and occupational asbestos, and this significance disappeared in the sub-analysis in which malignant mesothelioma was extracted from the 'all cancers' subgroup (SIR 1.11, 95% CI 1.00–1.24).

Table 3. Standardized incidence ratios (SIR) for selected cancers among those in the school cohort exposed only to environmental asbestos and the subgroups also exposed to household or/and occupational asbestos exposure.

	Environmental Asbestos Exposure			Household Asbestos Exposure			Occupational Asbestos Exposure			Occupational and Household Asbestos Exposure		
Cancer Site	**O**	**SIR**	**(95% CI)**	**O**	**SIR**	**(95% CI)**	**O**	**SIR**	**(95% CI)**	**O**	**SIR**	**(95% CI)**
All cancers (minus non-melanoma skin cancers) *	1180	1.05	(0.99–1.11)	257	0.95	(0.84–1.08)	**335**	**1.18**	**(1.06–1.31)**	49	1.12	(0.84–1.48)
All asbestos associated cancers *	339	1.03	(0.93–1.15)	73	0.96	(0.76–1.21)	**144**	**1.47**	**(1.25–1.74)**	21	1.33	(0.87–2.04)
Malignant mesothelioma	**11**	**5.09**	**(2.82–9.20)**	**4**	**22.77**	**(8.55–60.67)**	**20**	**8.67**	**(5.60–13.44)**	**3**	**10.38**	**(3.35–32.19)**
Lung, bronchus and trachea	135	1.01	(0.85–1.20)	32	0.93	(0.66–1.32)	**62**	**1.34**	**(1.05–1.72)**	7	0.88	(0.42–1.85)
Larynx	14	1.35	(0.80–2.28)	3	1.87	(0.60–5.79)	8	1.30	(0.65–2.60)	0	-	-
Ovary, fallopian tube and broad ligament	27	0.81	(0.56–1.19)	3	0.33	(0.11–1.02)	2	2.17	(0.54–8.67)	0	-	-
Pharynx	17	0.90	(0.56–1.44)	6	2.01	(0.90–4.47)	13	1.58	(0.91–2.71)	**4**	**4.24**	**(1.59–11.29)**
Stomach	22	1.19	(0.79–1.81)	2	0.55	(0.14–2.18)	8	1.38	(0.69–2.77)	1	1.20	(0.17–8.51)
Colon incl. rectosigmoideum	79	1.06	(0.85–1.32)	16	1.06	(0.65–1.73)	20	0.99	(0.64–1.54)	3	1.00	(0.32–3.09)
Rectum	40	0.87	(0.64–1.18)	9	0.83	(0.43–1.59)	14	1.27	(0.75–2.14)	3	1.26	(0.41–3.90)
Multiple cancers (>1 cancer)	100	0.96	(0.79–1.17)	22	1.00	(0.66–1.52)	30	1.20	(0.84–1.72)	3	0.63	(0.20–1.94)

Abbreviations: CI, confidence interval; O, observed number of cases, SIR, standardized incidence ratio; * Individuals with at least one cancer; 6 of the former school children with cancer (3 of them with an asbestos associated cancer) have no data on employments; Bold denotes statistically significant results.

Among those with an asbestos-related cancer, the SIR reached significance only in the subgroup combining environmental and occupational asbestos exposure. The SIR remained significant after extracting malignant mesothelioma from 'all asbestos associated cancers' (SIR 1.30, 96% CI 1.09–1.55).

Analysis by cancer type showed an increased SIR for malignant mesothelioma in all combinations of asbestos exposure and in those exposed only to environmental asbestos; the SIR was five-fold increased (SIR 5.09, 95% CI 2.82–9.20).

Cancer of the pharynx was significantly increased in the subgroup of environmental combined with occupational and household asbestos exposure (SIR 4.24, 95% CI 1.59–11.29). The SIR for lung cancer was significantly higher for those school children who had been exposed to both environmental and occupational asbestos (SIR 1.34, 95% CI 1.05–1.72).

3.3. Tobacco-Related Cancers

From the DLCR, we received data on 163 lung cancer cases (69.1%) from the school cohort and 2802 (66.6%) lung cancer cases from the reference cohort. In the DLCR, all lung cancer cases from both cohorts were registered as current or former smokers.

Asbestos-associated cancers are also tobacco-related, with the exception of malignant mesothelioma and most pathological types of ovarian cancer [24]. In a sub-analysis, the incidence of an asbestos and tobacco-associated cancer (colon, larynx, lung, pharynx, rectum, and stomach) was found to be significantly increased compared with the reference cohort group (SIR 1.11, 95% CI 1.02–1.21).

4. Discussion

Our study is the first to investigate the total burden of cancer following primarily environmental exposure to asbestos in childhood. In the present study, which provides follow-up data on cancer for almost 50 years, we investigated the incidence of overall primary cancer; multiple primary cancers; mesotheliomas; and cancers of the lung, larynx, pharynx rectum, stomach, and ovaries in children attending schools and living near a high-volume asbestos cement plant. Furthermore, we assessed risks from additional occupational asbestos exposure and family carry-home asbestos exposures. Overall, the incidence of cancer was increased. This increase was primarily driven by an increased risk of mesothelioma. However, in the subgroup of study participants who had been exposed to occupational asbestos, in addition to childhood environmental asbestos exposure, the risk of asbestos-associated cancers remained significantly elevated even when mesothelioma was excluded from the group.

Several previous studies have established that asbestos exposure is the dominant cause of malignant mesothelioma [25,26]. Malignant mesothelioma occurs even after low-level exposures, and apparently no safe level exists [27]. Only few studies have investigated the effect of childhood asbestos exposure and the risk of mesothelioma [10,28–37]. However, in a residentially crocidolite asbestos-exposed cohort from Wittenoom, Australia, the mesothelioma mortality rate was lower in those first exposed as children than in those first exposed at >15 years of age [31]. Similar results have been reported in a cohort of asbestos workers in Hong Kong [32]. In contrast, a British case-control study found the odds ratio (OR) to be higher in subjects who were younger than 20 years at first exposure than in subjects aged 30 years or more at first exposure. However, no increased OR was found for those living within one mile of a potential source (asbestos factory, disposal site, shipyard, or power plant) before 30 years of age [33]. In a study from New Caledonia (South Pacific), the risk of mesothelioma was found to be strongly associated with the use of whitewash using tremolite asbestos derived from local outcroppings. All cases' exposure had begun before the age of 16 [34]. Additionally, in a cohort employed by an Italian asbestos company producing mainly textiles, the standardized mortality ratio of mesothelioma was strongly related to time since first exposure [35]. Finally, in a French study, the effect of the total duration of asbestos exposure was found to decrease when age at first exposure and time since last exposure increased [36]. Accordingly, the majority of previous studies have

reported a higher risk of mesothelioma if subjects were exposed in childhood than if they were exposed later in life [28]. This is in line with the significantly increased risk of mesothelioma found in the asbestos-exposed school cohort in the present study. The low number of cases in the two subgroups with additional asbestos exposure from household and from both occupation and household could explain the wide confidence intervals and may also explain the higher risk in those who were also exposed to household asbestos.

For lung cancer, the risk has been found to increase linearly with the cumulative dose of asbestos exposure [38–40]. Studies investigating lung cancer risk have often involved relatively heavy asbestos exposure, and the risk at lower asbestos exposure levels has then been extrapolated from this reference threshold [41]. However, in a recent review and meta-analysis evaluating the association between environmental asbestos exposure and lung cancer, a significant increase in the risk of lung cancer was found for neighbourhood asbestos exposure [42]. We found the SIR for lung cancer to be significantly higher for the school children exposed to both environmental and occupational asbestos (SIR 1.34, 95% CI 1.05–1.72) than for the reference cohort, which suggests that the increase may originate in particular from occupational exposure, since no effect was observed in the groups without occupational exposure. However, a substantially higher frequency of tobacco smoking in the group exposed to occupational asbestos than in the group that was not exposed to occupational asbestos may also contribute to the observed increased lung cancer risk. The majority of lung cancer cases from both cohorts have been registered in the DLCR as former or current smokers, and there is well-established evidence for the additive or even multiplicative effect of asbestos exposure along with smoking on the risk of developing lung cancer [43,44]. However, due to lack of detailed tobacco data, a firm conclusion on this cannot be drawn.

Furthermore, along with tobacco smoking, alcohol drinking is also a risk factor for developing cancers of the pharynx, larynx, colon, and rectum [24,45]. A significantly increased incidence of stomach and laryngeal cancer was reported in the cohort of male workers employed at the Danish asbestos cement plant 1928–1984 [16]. Few other studies examining the correlation between asbestos exposure and laryngeal cancer have been able to determine a causal association between asbestos exposure and laryngeal cancer, and often studies have not accounted for confounding factors [46]. We observed an excess risk of laryngeal cancer, however, the incidence was not significantly increased compared with the reference cohort; nor did we have detailed data on confounding factors.

Results from a meta-analysis confirm the overall conclusion by the IARC, viz. that exposure to asbestos is associated with a modest, increased risk of stomach cancer [47]. However, in a previous study analyzing mortality from cancer of the lung and stomach in a town with asbestos deposits and in a town with asbestos processing, no significant differences could be attributed to environmental asbestos exposure [48]. This is consistent with the modest, but non-significantly increased, risk for stomach cancer we found in the school cohort.

The significant reduction in ovarian cancer observed in our study is not seen in previous studies [49]. Furthermore, the significance of our finding disappeared once the cohort was divided into asbestos exposure subgroups, which points to no protective effect of asbestos exposure as far as the incidence of ovarian cancer is concerned.

Few previous studies have investigated the influence of asbestos on developing multiple cancers [12,13]. To our knowledge, no studies have examined the incidence of developing multiple primary cancers after environmental asbestos exposure. The incidence of multiple cancers in the school cohort was similar to that of the reference cohort, both in the overall school cohort and when the cohort was divided into the asbestos exposure subgroups. This limits support for the hypothesis that the carcinogenic effect of asbestos could cause multiple cancers. Further research on this is warranted.

We acknowledge certain limitations of the present study. First, potential confounders such as smoking, alcohol consumption, and other lifestyle factors may have affected the incidence of certain cancers studied. Our study is registry-based, and the data analyzed did

not include these potentially confounding variables. Due to lack of relevant co-carcinogens or confounders, the risk estimates associated with asbestos exposure might be higher than the true estimates. Assessment of occupational exposure and household asbestos exposure by linkage to a JEM may result in non-differential misclassification and may attenuate the SIR towards the null.

Our findings are based on data from a large population. This, as well as the very long follow-up time and the use of long-established, practically complete and objective, national registers, provides valid and robust results. Thus, for settings similar to Aalborg, we find the external validity of this study to be high.

5. Conclusions

Both the incidence of malignant mesothelioma and the overall cancer incidence were significantly increased among our cohort of former school children who attended school and lived near a large asbestos cement plant. Our results confirm the strong association between environmental asbestos exposure and malignant mesothelioma. This study indicates that not only does occupational asbestos exposure pose an increased risk of cancer, but environmental asbestos exposure in childhood may also have deleterious effects. Asbestos remains in use in several countries around the world, and more attention should be paid to prevent the carcinogenic effects of asbestos from environmental, occupational, and household exposure to asbestos. The most effective prevention is to stop the use of asbestos. Further studies are warranted.

Author Contributions: Ø.O. conceived the study. J.H. collected, cleaned and coded raw data from registries. J.H. constructed the asbestos JEM. S.B.D. performed the statistical analyses and drafted the manuscript in collaboration with E.T.W., O.D.R. and Ø.O. All coauthors have assisted with interpretation of the findings and revised the manuscript critically. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: According to Danish law, register-based studies do not need approval by ethical and scientific committees, nor informed consent.

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Exhibit E

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ORIGINAL ARTICLES AND REVIEWS

Early mortality from malignant mesothelioma in Italy as a proxy of environmental exposure to asbestos in children

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Abstract
Malignant mesothelioma (MM) is a rare neoplasm caused by asbestos. Mortality from MM in ≤50 years old people, considering the long latency, is likely related to asbestos exposure in childhood. Mortality from MM (C45, ICD10 code) is described among ≤50 years (ys) old people in Italy, in 2003-2016. National and regional Standardized Rates (SRs) were computed by age-class. The North-South trend of regional SRs, increasing in >50ys age-class, showed a flat cline in ≤50ys old people. Municipal Standardized Mortality Ratios (SMRs) were computed, with respect to regional figures, for ≤50 ys old population. In Italy, 487 people ≤50 ys old died from MM, in 2003-2016 (2.5% of all MM deaths), corresponding to 35/year. The highest SMRs were observed in Northern Regions, the most industrialized areas. Exceeding SMRs were found in 10 municipalities where former asbestos-cement plants, shipyards, and a quarry contaminated by fluoro-edenite fibres were present. Early mortality from MM, proxy of childhood environmental asbestos exposure, deserves particular concern.

Key words
- epidemiology
- mesothelioma
- mortality
- asbestos
- young adults

INTRODUCTION

Malignant mesothelioma (MM) is a rare neoplasm, originating from mesothelial cells of serous cavities (pleura, peritoneum, pericardium, and vaginal tunic of the testicle). Pleural MM represent about 80% of all MM cases. MM is highly lethal and characterised by a long period of latency (about 40 years and over) [1]. More than 80% of MM cases are attributable to asbestos exposure. All asbestos types are ascertained carcinogenic to human (Group 1), causing with sufficient evidence mesothelioma and lung, larynx and ovary cancers. A positive association with cancers of pharynx, stomach and colon-rectum was also reported [2]. Erionite, a naturally occurring fibrous mineral, was also confirmed to be an ascertained carcinogenic to human, causing mesothelioma [2]. In addition, in 2017 IARC defined fluoro-edenite, a previously unknown asbestos-like fibrous mineral, as carcinogenic to humans (Group 1), on the basis of the ascertained causal link with MM [3].

The number of deaths from MM is currently used to estimate the population burden of this neoplasm, in light of its high lethality. Incidence data, as a matter of fact, are not always available. Odgerel and colleagues estimated the global burden of MM in the range from 36,300 to 38,400 deaths per year, in a 20 year-period (1994-2014), considering 230 countries [4].

Asbestos is one of the most widespread occupational carcinogens: the World Health Organization (WHO) has estimated that around 125 million people worldwide are currently exposed to asbestos at workplace (www.who.int/ipcs/assessment/public_health/asbestos/

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en/). The Global Burden of Diseases (GBD) study estimated about 63% of occupational cancers attributable to asbestos in 2017 at global level, including 27,000 cases of mesothelioma [5].

Estimating the burden of MM cases due to non-occupational exposure is particularly difficult, though the risk of pleural mesothelioma caused by the residence near asbestos fibres sources (quarries, asbestos-cement plants) is known [1, 6]. Some estimates show that about 20% of MM cases at global level could be caused by non-occupational exposure to asbestos [6].

Italy was one of the main producers and importers of raw asbestos until the ban in 1992 [7]. In Italy, in 2003-2014 period, 16,086 persons died from MM, corresponding to 1,340 per year. Temporal trends show an increase of mortality from MM, in particular from pleural MM among men, in the last years [8]. The most recent report of the Italian Registry of Mesothelioma (ReNaM) identified 27,356 incident cases of mesothelioma from 1993 to 2015, corresponding to about 1,600 incident cases per year in the last period [9]. Information on the exposure context was available for 21,387 cases (78.2%): among these, 70.0% experienced occupational exposure (certain, probable, possible), 4.9% domestic and 4.4% environmental exposure, meanwhile for 1.5% of them the asbestos exposure was related to leisure or hobby activity. For 20% of cases, asbestos exposure was unlikely or unknown [9]. On the basis of exposure ways reported in ReNaM database, clusters of MM cases due to environmental exposure were mainly related to the presence of asbestos-cement plants, shipbuilding and repair activities and soil contamination [1]. Regarding the last asbestos exposure source, local investigations reported an exceeding risk of MM in some Italian areas with naturally asbestos fibres presence [10, 11]. MM cases were reported in excess in an area of Pollino Mount (Basilicata Region, Sothern Italy), where naturally serpentine and metabasite outcrops, containing asbestos fibres (namely, tremolite, actinolite and chrysotile), occurred [10]. In early 2000s, pleural and peritoneal malignancies were found in excess in some municipalities of Upper Susa Valley (Piedmont Region, Northern Italy), where tremolite asbestos in rocks surfaced by natural ground erosion or originating from construction activities [11]. MM cases environmentally exposed were reported in areas close to chrysotile and fluoro-edenite fibres containing quarries [12, 13]. An investigation focused on female MM cases found that non-occupational case-list of ReNaM is characterized by the prominence of women [14].

The improvement of early diagnosis of MM and the establishment of registries recording people exposed to asbestos are among the public health actions recommended by WHO (www.who.int/ipcs/assessment/public_health/asbestos/en/). Moreover, during the Sixth Ministerial Conference on Environment and Health, the 53 countries of WHO European Region committed to develop national programs to eliminate asbestos-related diseases, in agreement with the objectives of 2030 UN Agenda for Sustainable Development [15].

The issue of health risks originating from asbestos exposure in children is rarely addressed, mainly due to the low number of young mesothelioma cases and to the difficulties to detect a causal role of past exposure occurred during childhood. A systematic review on the age at first exposure to asbestos and the risk of asbestos-related diseases reported the studies published up to July 2012 [16]. The object of the review was highlighting the difference in MM risk, on the basis of the age at first asbestos exposure. Six studies reporting risk of MM mortality by age-class, childhood included, among occupational and environmental asbestos exposed subjects [17-22] were considered. Four studies found the highest risk in subjects aged 15 years (ys) or less at first exposure [17-20], meanwhile the other one reported a lower risk in subjects exposed at young age (less than 20 ys) than in adulthood [21]. The subjects exposed at birth showed the highest risk in the only study that included birth as age at first exposure [22]. Regarding the highest risk age at first asbestos exposure, the results of all studies, also restricting to only residential exposure investigations, were not consistent. The Authors concluded that because of the low number of the studies and their limitations the results are inconclusive and further studies are needed [16].

More recently, some cohort studies analysed the risk of MM among populations residentially exposed to asbestos in childhood. Dalsgaard and colleagues performed a cohort study on the incidence of MM in former children attending four schools located near an asbestos-cement plant in Aalborg [23]. The median age at diagnosis (similar in school and reference cohort) was 61 years (34-74 ys). MM was diagnosed more than 30 years after the school attendance in the majority of cases. Higher risk (Hazard Ratio: HR) in school cohort, adjusted for occupational and familial occupational exposure, was found and the results were confirmed also restricting the analysis to the subjects without occupational or familial occupational exposure. Similar HRs were shown in men and women, with M/F ratio in the school cohort equal to 1.2:1, as assumed for environmental exposure. The results suggested that childhood environmental exposure is an important risk factor for MM in late life [23]. Increased risk (OR = 3.3; 95% CI: 1.4-7.7) in subjects attending grammar school in Casale Monferrato, where the largest Italian asbestos-cement plant operated, was also reported in a case-control study on pleural MM incidence [24].

The risk of asbestos-related diseases in the population living near the Wittenoom crocidolite mine in Australia was investigated in several studies [21, 25, 26]. In the cohort analysis after 30 years and more of follow-up, increased incidence and mortality risk from several cancers, including mesothelioma, were found among adults living at Wittenoom in childhood (aged <15 ys) [25]. However, in a subsequent analysis of MM incidence, difference in risk between the subjects exposed in childhood (<15 ys) and adulthood was not observed [26], confirming the previous findings [21].

In 2017 a study on the association between residential exposure to Libby amphibole asbestos (LAA) prior to age 18 and respiratory symptoms in late life (median age: 25 ys) was published [27]. Pleural or interstitial changes

on chest x-ray or HRCT were not found, but several respiratory symptoms, including self-reported pleural chest pain, among young adults were associated to childhood environmental exposure to LAA and were highlighted as a possible indicator of future respiratory diseases [27].

The Surveillance, Epidemiology and End Results (SEER) database reported a lower M/F rates ratio for MM cases aged under 65, with respect to those aged 65 and over [28].

Few studies on MM risk have been performed in Latin-American countries. A recent mesothelioma case-series in the municipality of Sibaté, where a major Colombian asbestos-cement facility is located was published. Some of the characteristics of the observed MM cases are represented by the early age at diagnosis, the sex-ratio approaching one and the absence of occupational exposure to asbestos, thus suggesting a major role of environmental exposure [29].

In Italy, the mortality from pleural mesothelioma by age-class was reported for 2003-2009 period [30]. In 0-39 age-class, 8 male and 7 female deaths were observed, corresponding to 0.01 (95% CI: 0.005-0.02)/100,000 in men and 0.01 (95% CI: 0.004-0.02)/100,000 in women. In the same period the corresponding rate in the overall population was 2.8 (95% CI: 2.7-2.9) and 0.8 (95% CI: 0.8- 0.9) /100,000, in men and women, respectively. The M/F ratio in 0-39 year age-class was equal to 1, meanwhile in the older age-classes male death rate was about 3-fold that of females rate: M/F = 3.4 in subjects aged 40-75 and M/F = 3.3 in 76-99 age-class [30].

The incidence of MM cases in Italy, in different age-classes by modality of exposure, on the basis of ReNaM database, was reported in Marinaccio, *et al.* 2015 [1]. MM cases aged less than 45 ys at diagnosis were rare, accounting for 2.4% of all cases recorded in 1993-2008 period (15,845 MM cases). Significantly, lower mean age at diagnosis was observed in non-occupationally exposed, in particular in those with an environmental exposure, compared to the cases exposed in occupational settings (67.2 and 66.1, respectively, *vs* 68.1). The mean age at first exposure was significantly lower in subjects environmentally exposed than in those occupationally exposed (17 *vs* 22.5 years, p value <0.001) [1].

Considering the long period of latency, the high mortality rate and the high attributable fraction to asbestos exposure, early deaths from MM could represent a *proxy* of exposure in childhood. Studying the early occurrence of mesothelioma has relevant public health and ethical implications in terms of health protection by unintentional exposure to environmental hazards in children, also considering the hypothesis of a highest vulnerability to environmental risk of this age-class population [31, 32]. Temporal and spatial distributions of early MM deaths could contribute in estimating the health impact of non-occupational exposure to asbestos in childhood. This is the case, for example, of the children living in areas contaminated by asbestos fibres or indirectly exposed to asbestos in domestic context, because of occupational activities of the parents.

In Italy, a preliminary analysis of early malignant pleural neoplasms (MNP) mortality, showed 1,594 early deaths (≤50 ys) from MNP in 1980-2010 period (55 per year on average, annual standardized rate = 0.2/100,000) and identified 147 municipalities where early mortality from MNP was significantly higher than the expected (mainly located in Regions mostly affected by activities involving asbestos exposure) [33].

The present study describes mortality from MM in Italy in people younger than 50 years (≤50 ys) and its geographical distribution, as a possible marker for environmental exposure to asbestos in children.

MATERIALS AND METHODS

This study is based on data of mortality from malignant mesothelioma (MM) at municipal level that are included in the cause-specific mortality database managed by the Statistical Service of the National Institute for Health, and provided by the Italian National Institute of Statistic (Istat).

Mortality from MM was analysed in a 14 year-period (2003-2016), the most recent years available at the beginning of the study, from ICD10 revision application. The MM deaths included in the study were all those recorded in the specific diagnostic category of malignant mesothelioma C45 (ICD-10).

National and regional standardized mortality rates (SR, direct method, 2013 European population as reference: https://ec.europa.eu/eurostat/web/products-manuals-and-guidelines/-/KS-RA-13-028) and their 90% Confidence Intervals (90% CI), in the population ≤50 and >50 ys old, were computed by gender.

Standardized Mortality Ratios (with 90% CI) in the subpopulation ≤50 ys old were computed for each of the 21 Italian Regions and Autonomous Provinces and for the 8,047 Italian municipalities, using national and regional age-class and gender specific rates as references, respectively. 90% CIs were estimated based on Poisson's distribution, if the observed cases were less than 100, otherwise on Byar method. Considering the low number of cases, SMRs were computed for the overall population, including both men and women, to reach a less broad CI.

RESULTS

In Italy, during 2003-2016 period, 487 persons ≤50 ys old died from MM (34.8 cases/year, on average), corresponding to 0.096 cases/100,000 inhabitants. These cases represent 2.5% of all deaths from MM in the same period (19,315 cases). *Table 1* shows the number of all MM cases and the corresponding standardized rates (SR), by age-class (≤50 and >50 ys) and gender.

The number of deaths from MM, by site, age-class and gender is reported in *Table 2*. The percentage of peritoneal MM, with respect to all MM deaths, is higher in ≤50 ys old people than in >50 ys old, among both sex (12.5% *vs* 3.8% in men and 16.7% *vs* 5.7% in women). Among young adults, the percentage of pleural MM, with respect to all MM, in men is higher than in women (73.5% *vs* 66.7%); in the latters, the percentage of peritoneal and other MM, equal to 16.7%, is higher than in male population.

The ratio of male to female standardized rates (SRm/SRf) is equal to 1.8 in the young sub-population (≤50

Table 1
Mortality from malignant mesothelioma: cases and age-standardized death rate, by age-class and gender. Reference: 2013 European population. Period: 2003-2016

Age (years)	Cases	ASR (90% CI)
	Men	
≤50	313	0.16 (0.14-0.18)
>50	13,511	9.34 (9.21-9.18)
	Women	
≤50	174	0.088 (0.074-0.105)
>50	5,317	2.73 (2.67-2.80)
	Overall	
≤50	487	0.12 (0.11-0.14)
>50	18,828	5.57 (5.50-5.63)

ASR: Age Standardized death Rate (n. deaths/100,000 inhabitants); 90% CI: Confidence Interval.

Table 2
Mortality from malignant mesothelioma (MM), by site, sex and age-class: number of cases and percentage with respect to all MM deaths. Period: 2003-2016

Cause of death	ICD	Men cases (%)	Women cases (%)	Overall cases (%)
Age ≤50				
Mesothelioma of pleura	C45.0	230 (73.5)	116 (66.7)	346 (71)
Mesothelioma of peritoneum	C45.1	39 (12.5)	29 (16.7)	68 (14)
Other mesothelioma	C45.2-C45.9	44 (14.1)	29 (16.7)	73 (15)
Mesothelioma (all)	C45	313 (100)	174 (100)	487 (100)
Age >50				
Mesothelioma of pleura	C45.0	11080 (82)	4246 (79.9)	15326 (81.4)
Mesothelioma of peritoneum	C45.1	514 (3.8)	303 (5.7)	817 (4.3)
Other mesothelioma	C45.2-C45.9	1917 (14.2)	768 (14.4)	2685 (14.3)
Mesothelioma (all)	C45	13511 (100)	5317 (100)	18828 (100)

ys) and 3.4 in older population (>50 ys), in overall period 2003-2016. *Figure 1* shows the national M/F ratio by year.

The geographical trend of regional MM mortality standardized rates, by Istat macroarea (North-West, North-East, Centre, South and Islands) and age-class is shown in *Figure 2*. In ≤50 ys old population the cline is flat, meanwhile a decreasing North-Southern trend is observed in overall and >50 ys old people *(Figure 2)*.

Regional SMRs from MM in young population (≤50 old) are showed in *Table 3* and *Figure 3* reports the geographical distribution.

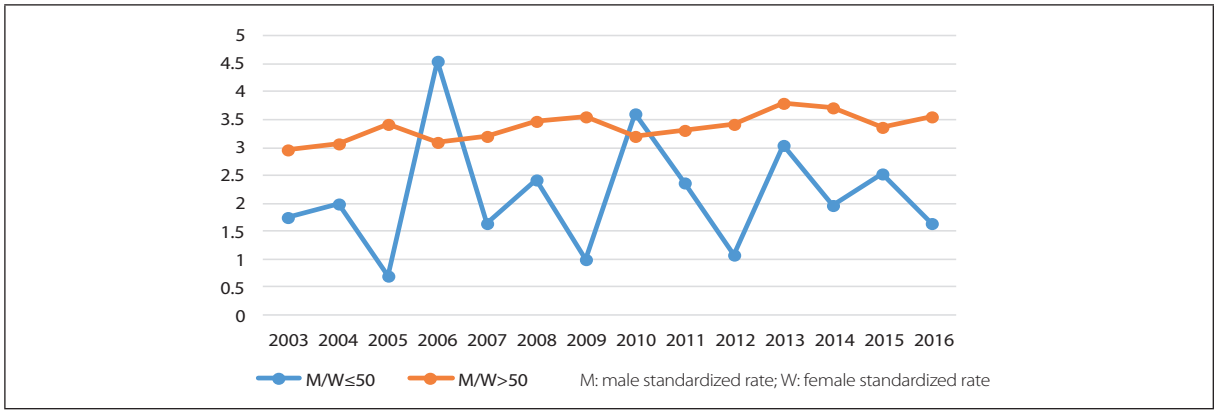

Figure 1
Mortality from malignant mesothelioma. Annual trend of sex ratio (male standardized rate/female standardized rate), by age-class. Period: 2003-2016.

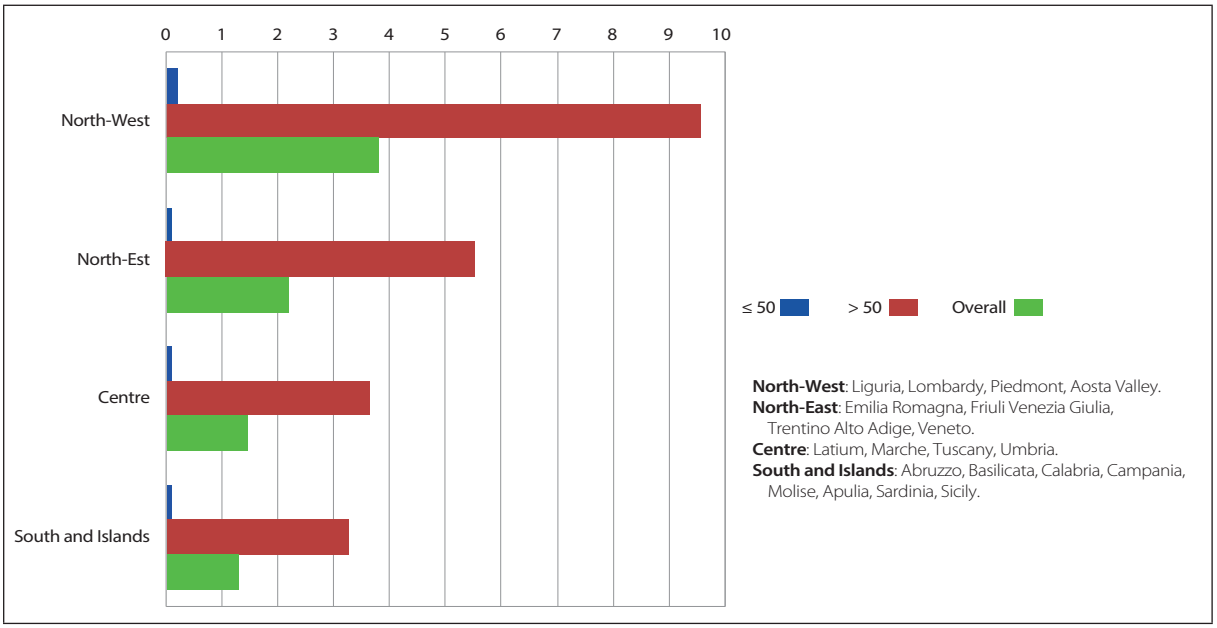

Figure 2
Mortality from malignant mesothelioma. Regional standardized rates (/100,000), by Istat macroarea (North-West, North-East, Centre, South and Islands) and age-class. 90% Confidence Intervals. Period 2003-2016.

Table 3
Mortality from malignant mesothelioma, in ≤50 years old population. Standardized Mortality Ratio by Region. Reference: National Rate. Period: 2003-2016

Region	OBS	SMR (90% CI)
Piedmont	73	204.0 (168.4-247.3)
Aosta Valley	1	93.2 (20.8-417.7)
Lombardy	115	141.1 (121.1-164.5)
Bolzano	5	120.3 (58.6-247.1)
Trento	1	23.1 (5.16-103.8)
Veneto	25	60.9 (43.9-84.4)
Friuli-Venezia Giulia	5	49.7 (24.2-102)
Liguria	18	141 (95.9-207.2)
Emilia-Romagna	35	97.7 (74.1-129)
Tuscany	28	93.7 (68.8-127.7)
Umbria	5	71.8 (34.9-147.5)
Marche	10	81.3 (48.6-136)
Latium	34	72.6 (54.8-96.2)
Abruzzo	4	37.9 (17.0-84.5)
Molise	2	79.7 (26.4-241)
Campania	46	99.7 (78.3-126.6)
Apulia	26	81.1 (58.8-111.9)
Basilicata	2	42.9 (14.2-129.6)
Calabria	12	77.5 (48.4-124)
Sicily	35	89.4 (67.8-118)
Sardinia	5	35.8 (17.4-73.5)

OBS: Observed cases; SMR: Standardized Mortality Ration; CI: Confidence Interval.

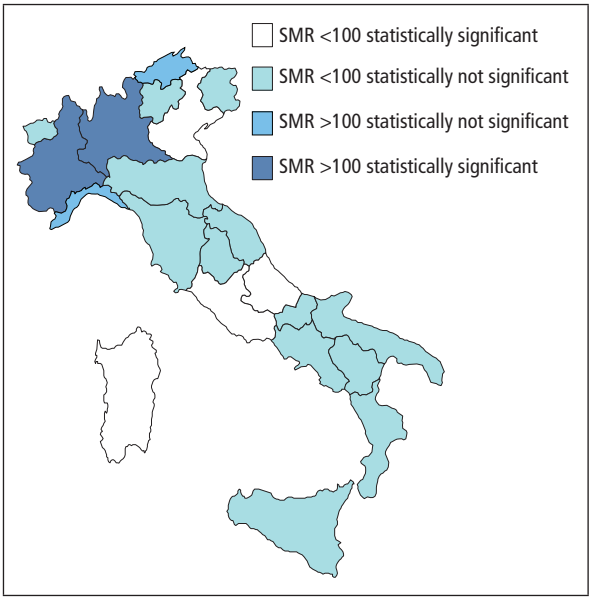

Figure 3
Mortality from malignant mesothelioma, in ≤50 years old population. Geographical distribution of Standardized Mortality Ratio (SMR), by Region. Period: 2003-2016.

The early mortality (≤50 ys) from MM at regional level as compared to national rates, show higher risks in some Northern Italian Regions: Piedmont and Lombardy display SMRs significantly higher than 100, Liguria and Bolzano Province have rates higher than the National one, even if the CI lower limit is <100.

In the analysis at municipal level, 357 out of the 8,078 Italian municipalities showed at least one MM death ≤50 years old, in the study period. In ten municipalities

Municipality	OBS	SMR (90% CI)
La Spezia	3	396.4 (158.4-991.8)
Stradella	3	3132.2 (1251.8-7837.4)
Quattro Castella	3	2728 (1090.2-6825.8)
Torre Annunziata	3	927.01 (370.5-2319.6)
Alessandria	4	538.2 (241.6-1198.8)
Biancavilla	4	2324.2 (1043.5-5177.1)
Monza	4	393.7 (176.8-877)
Broni	6	8095.0 (4186.0-15654.2)
Genova	11	229.9 (140.7-375.7)
Casale Monferrato	17	5805.9 (3906.1-8629.7)

OBS: Observed Cases; SMR: Standardized Mortality Ratio; CI: Confidence Interval.

Figure 4
Early mortality from malignant mesothelioma (≤50 years old). Municipalities with SMR and 90% Confidence Interval Lower Limit >100, based on at least 3 observed cases. Period: 2003-2016.

a statistically significant excess risk (based on at least 3 cases) was observed *(Figure 4)*.

DISCUSSION

In Italy, 2.5% of all deaths from MM occurred in ≤50 years old people (487 cases in 14 years, 2003-2016), corresponding to around 35 deaths per year, on average. Considering the long period of latency of the disease and the high attributable fraction to asbestos exposure, these deaths could be probably due to asbestos exposure occurred in childhood.

Several previous investigations, reporting excesses of early mortality from MM in people exposed to asbestos in childhood [23-26], corroborate this hypothesis. For this reason, localized excesses of MM mortality in ≤50 ys old people, could also be used as a sentinel event of past, or current, contexts of environmental exposure to asbestos.

Considering the causal link between MM and fibres [2, 3], we highlight that no information on the presence of erionite outcrops either erionite exposure contexts for the population in Italy has been reported. Contexts of exposure to fluoro-edenitic fibres were detected in a specific area that will be considered in the comments of the present findings.

The lower MM mortality ratio of male to female in young age-class, compared to that in >50 ys old population (1.8 *vs* 3.4), corroborates the hypothesis of a non-occupational asbestos exposure in early MM cases. This hypothesis is confirmed by data from ReNaM, that showed a significantly higher F/M gender ratio in environmentally exposed cases than in overall and occupationally exposed cases (1.19 *vs* 0.38 and 0.14, respectively) [14]. MM Female/Male rate ratio about 1:1 in under 65 people was reported also in US population [28] and among MM cases residentially exposed to asbestos in childhood, in Aalborg [23].

In addition, the percentage of incident cases reported in ReNaM database with a history of occupational exposure is lower among subjects ≤50 years than in >50ys old (37% *vs* 56%); the proportion of MM incident cases with environmental/familial exposure is around two-fold significantly higher in the young (≤50 ys) with respect to older cases (16% *vs* 8%) [9]. Furthermore, ReNaM findings provide evidence of a percentage of unknown or unlikely modalities of exposure higher in young MM patients (≤50 ys old at diagnosis) than in older cases (24.6% and 15.6%, respectively) [9].

The analysis of mortality by MM site, age-class and gender *(Table 2)* highlighted a higher percentage of peritoneal MM in young adult (≤50 old) than in >50 old people, among both gender (12.5% *vs* 3.8% in men and 16.7% *vs* 5.7% in women). In addition, our evaluation showed that in both age-classes the percentage of peritoneal MM, with respect to all MM deaths, is higher in women than in men. In a previous investigation on peritoneal mesothelioma risk in Italy, based on multiple-causes mortality and ReNaM incidence database, the 0-44 years age group had a higher proportion of incident peritoneal MM cases (6.2%) than of pleural MM (2.4%). In the same age group, 34.7% of deaths and 44.4% of incident cases for peritoneal MM occurred among women [39]. The issue of misclassification of ovarian cancers in peritoneal mesothelioma, as

well as of other abdomen contiguous tumours, has been discussed in recent papers [39-42].

The analysis of regional SMR distribution showed the highest mortality risk from MM among young adults in some Northern Regions. The same geographical pattern was observed in the general population mortality from MM, following the industrial geographical distribution in the country, with the highest industrialization rate in Northern Italy [8, 30, 38]. In particular, the former Italian largest asbestos-cement plants were located in Broni and Casale Monferrato, Lombardy and Piedmont Region (North-West) respectively. In Liguria Region (North-West Italy), several shipyards and naval industries are still operating. The high SMR found in Bolzano Province has never showed before, and deserves further in-depth analysis.

The presence of these activities could explain the geographical North-South trend observed in overall and >50 ys old people, with the highest SRs in North-West macroarea. The flat cline observed in young adults (≤50 ys old) corroborates the hypothesis of a less contribute of occupational exposures in early MM mortality.

At municipal level, significant exceeding SMRs (based on 3 or more observed cases) in young adults (≤50 ys old) were observed in municipalities with known asbestos sources: asbestos-cement plants (Broni and Stradella, Casale Monferrato), shipbuilding and repair activities (Torre Annunziata, La Spezia and Genova) and a quarry contaminated by fluoro-edenite fibres (Biancavilla), characterized by a high mortality from MM in the general population also [8]. The presence of the same asbestos sources was related to clusters of non-occupationally exposed MM incident cases [1].

The case of Biancavilla municipality (Sicily Region, South Italy) represents an example of appropriateness of using early mortality as a marker of residential asbestos exposure in children. A high risk of mesothelioma in the population living in this municipality related to environmental exposure to fluoro-edenitic fibres contained in the stone quarry located in the municipality has been highlighted, since the late Nineties [34]. The epidemiological investigations performed in Biancavilla, corroborated by animal studies, contributed to the evaluation by IARC of the carcinogenicity of fluoro-edenite [3]. In 1980-2010 period, 6 deaths from MNP *vs* 0.6 expected were observed in this municipality (SMR = 1,003, CI 90%: 437-1,980) among people aged 50 ys or less. Extending the analysis to municipalities located wit:hin a radius of 10 km from Biancavilla, the number of MNP deaths rose to 11 (SMR = 367, CI 90%: 206-608) [35]. Same results were found by the analysis of MM incident cases living at the diagnosis in Biancavilla, based on Regional Operating Centre of ReNaM database. A higher value of Standardized Incidence Ratio (SIR), with respect to regional figures, was shown in people aged less than 50 years (5 cases, SIR = 2,134, 95% CI: 693-5,000) than among older people (19 cases, SIR = 474, 95% CI: 285-739), even if based on a low number of cases [13].

Regarding Alessandria, Monza and Quattro Castella, the other municipalities reported in *Figure 4*, no specific etiological hypotheses have so far been raised. An excess of mortality from pleural mesothelioma, in the male population, was previously observed in Quattro Castella [36]. In these contexts, *ad hoc* in-depth studies appear to be warranted.

In spite of the uncertainty of the computed estimates, due to the low number of observed and expected cases, these results deserve specific concerns, in view of the rarity of the phenomenon and the ethical implications, considering the possibility of a childhood exposure to environmental risks.

Some limitations of the present study need to be discussed.

A limitation is related to the use of mortality data in the detection of mesothelioma cases. A possible underestimate of MM cases in asbestos occupational cohort studies using mortality data, with respect to incidence data, was debated [37]. Misclassification caused by the use of death certificates was discussed also in previous papers on the surveillance of mesothelioma mortality in Italy [30, 38]. The use of the 10th revision ICD code, available in Italy at national level since 2003, including the specific morphological code of malignant mesothelioma reduces the possible misclassification. In addition, the high mortality rate of the disease mitigates the possible bias, but a remaining effect could not be ruled out, and some prudence in the interpretation of the data is appropriated.

Moreover, a limitation could be represented by the use of the residence at death as a *proxy* of the childhood residence. The geographical analysis, performed in order to identify the areas with possible asbestos sources, was carried out on the basis of the residence transcribed in death certificate (as Istat database) while, taking into account the long period of the latency, the place of residence during childhood, where exposure to asbestos probably occurred, might have been different.

In addition, regional and municipal SMRs have been computed for men and women combined to improve the precision of the estimates, considering the ratio F/M close to one in early MM mortality. Studies analysing the distribution of early MM deaths by site and gender, with suitable methods, appear appropriated.

Further investigations, based on the integration of MM mortality and incidence data, the latter from ReNaM database, could reduce parts of these limitations and furnish a useful focus on this issue. The analysis of early MM occurrence, by site of MM, sex and exposure modality, based on individual database, appears of particular concern, taking into account also the specific F/M ratio among young adults.

CONCLUSION

The analysis of early mortality from MM showed that in Italy, in 2003-2016 period, 487 people ≤50 ys old died from MM, corresponding to 2.5% of all MM deaths, due to a likely non-occupational asbestos exposure in childhood.

Geographical distribution highlighted regions and, particularly, municipalities with the highest risks of MM mortality for this specific population age group.

These signals, though characterised by uncertainty, require to implement specific public health and environmental remediation actions, and further in-depth in-

vestigations, in the light of their ability to identify past, or still on-going, environmental sources of exposure that could impact on childhood population.

The findings of the present study provide evidence of the usefulness to use early MM mortality data as a *proxy* of asbestos exposure in people affected in young age, particularly where individual assessment of exposure is not available. This possibility might be common in low- and middle-income countries where environmental exposure to asbestos in children is a critical issue [43] and where suitable experiences of surveillance systems of mesothelioma incident cases, including the individual evaluation of the modalities of exposure, still lack.

The use of the adopted methods, based on mortality data, to replicate the study in other countries could give an important information on the environmental exposure to asbestos, at global level.

Author's contributions statement

Conception: II, LF, PC, SC, GM, CB, AZ; Acquisition and analyses of data: GM, MDS; Interpretation of data: AB, AM, AZ, CB, CM, II, LF, PC, SC; Writing-Original draft: LF, II; Writing: Revising and final approval: LF, AB, AM, AZ, CB, CM, GM, MDS, PC, SC, II.

Conflict of interest statement

The Authors declare that neither they nor their Institutions have financial or personal relationship with other people or organizations that could inappropriately bias conduct and findings of the study.

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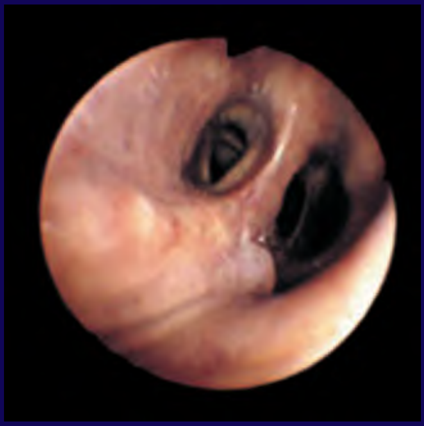
Exhibit F

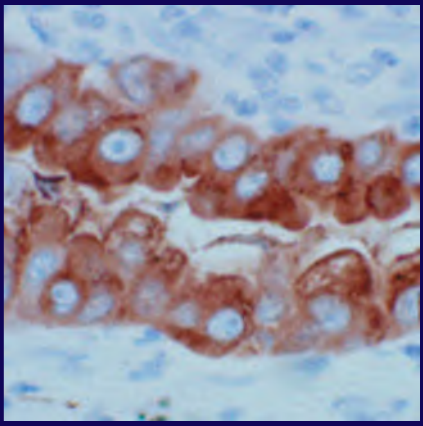
World Health Organization Classification of Tumours

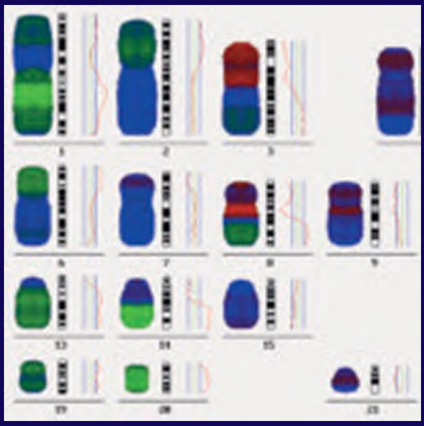
Pathology & Genetics

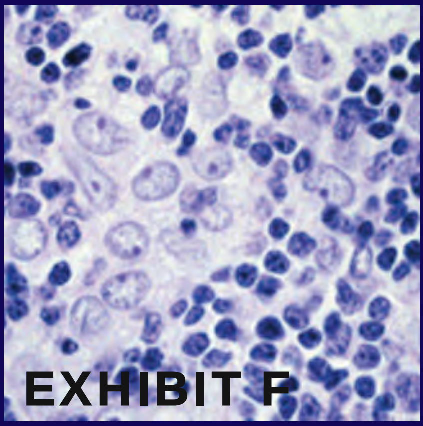
Tumours of the Lung, Pleura, Thymus and Heart

Edited by William D. Travis, Elizabeth Brambilla,
H. Konrad Müller-Hermelink and Curtis C. Harris









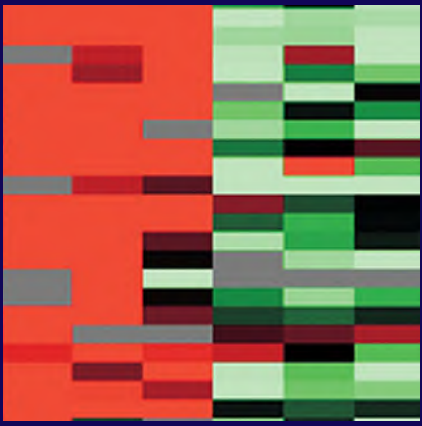


EXHIBIT F

WHO Classification Tumours of the Lung, Pleura, Thymus and Heart

IARC

World Health Organization Classification of Tumours

WHO OMS

International Agency for Research on Cancer (IARC)

Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart

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Pericardial tumours

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Solitary fibrous tumour

Definition
An uncommon, spindle-cell, fibroblastic tumour which often shows a prominent haemangiopericytoma-like vascular pattern.

ICD-O code
Solitary fibrous tumour 8815/1

Synonyms
Benign mesothelioma, fibrous mesothelioma, submesothelial fibroma

Localization
The most common locations, outside the pleura, include the head and neck, especially orbit, soft tissue, especially abdomen, extremities, and meninges {233,1384,1473}. As with any lesion common to the pleura, there have been examples of solitary fibrous tumour reported in the pericardium and rarely within the heart.

Clinical features
Clinical features are related to pericardial mass effect.

Macroscopy
Solitary fibrous tumours tend to be well-circumscribed, firm, fleshy or white although diffuse mesothelial surface involvement has been described.

Histopathology
Histologic variability is the rule and multiple growth patterns have been described. Most tumours will have a predominant monomorphic spindle cell pattern resembling low-grade fibrosarcoma although broad tumour cell fascicles are rare. Areas of hypercellularity typically alternate with those that are less cellular. The less cellular areas can by myxoid or contain abundant collagen {459}. Typically the nuclei of tumour cells are closely apposed to collagen bundles. A haemangiopericytoma-like vascular pattern may be conspicuous, present in a small portion of the lesion, or absent. The differential diagnosis includes other monomorphic spindle cell tumours, including neurogenic tumours, spindle cell mesotheliomas, monophasic synovial sarcoma, and fibrosarcoma {1311}. Recently, desmoid tumour of the pleura has been added in the list of differential diagnostic considerations {2151}. See pleural section for additional information.

Immunoprofile
Solitary fibrous tumours are CD34 and bcl-2 positive. They are consistently negative for epithelial markers, muscle specific actin, desmin, CD31, CD117 (c-kit), S-100 protein calretinin, and inhibin {596,772,1473,2127}.

Differential diagnosis
Sarcomatous mesotheliomas of the pericardium are distinguished from solitary fibrous tumours by their diffuse growth pattern, and keratin and calretinin reactivity. On the other hand, solitary fibrous tumour may closely mimic monophasic synovial sarcoma and low- grade fibrosarcoma. Fibrosarcoma tends to be more architecturally monomorphic and negative for CD34. Monophasic synovial sarcoma has higher grade cytology, plumper nuclei and shows focal keratin reactivity. Endometrial stromal sarcoma, and metastatic granulosa cell tumour may be excluded by negative reactivity for cytokeratin, estrogen and progesterone receptors, and inhibin.

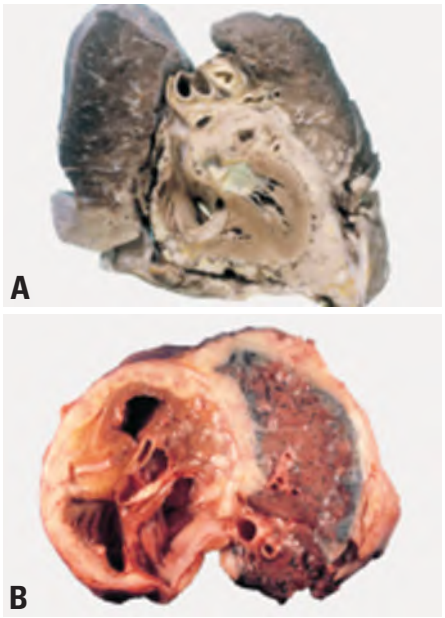

Fig. 4.39 Mesothelioma of pericardium. **A** Note the extensive tumour encasing the pericardium. **B** In many cases, the pericardial mass is in continuity with pleural mesothelioma.

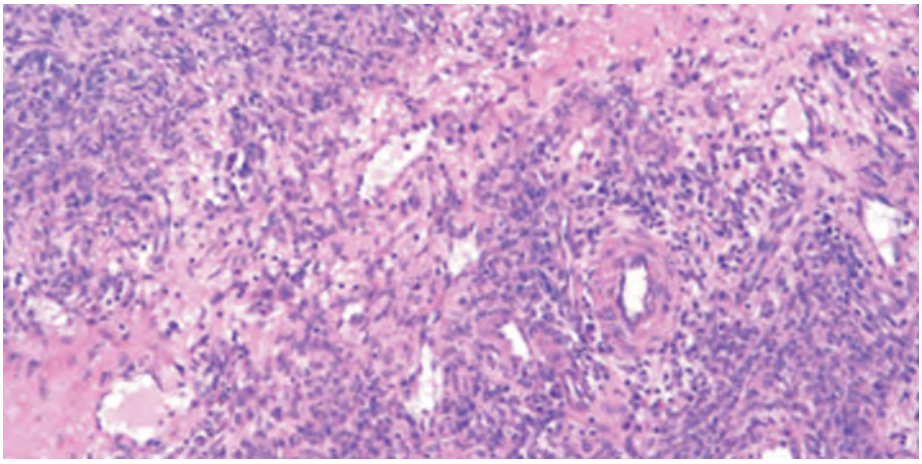

Fig. 4.40 Localized fibrous tumor of the mesothelium is identical in appearance to those of the pleura. Note the spindle cell growth with prominent vascularity and variable cellularity.

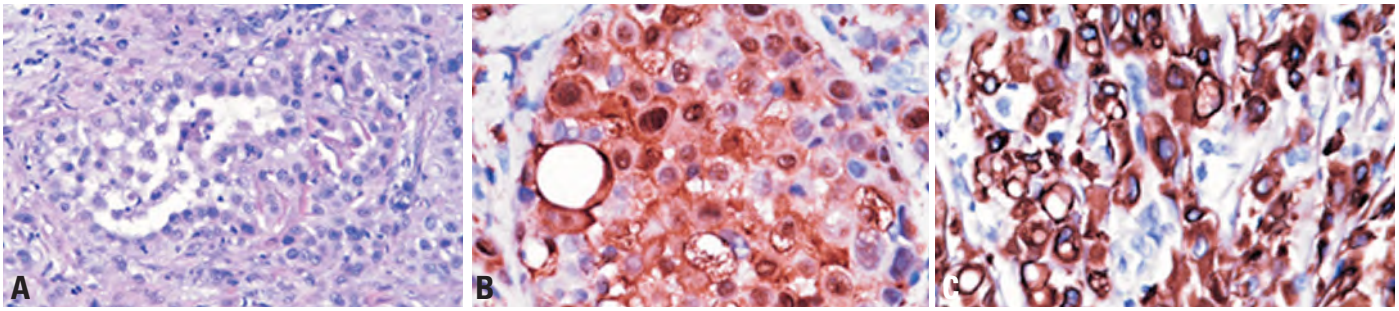

Fig. 4.41 Pericardial mesothelioma. **A** The majority of pericardial mesotheliomas are epithelioid. **B** Strong expression of calretinin. **C** Strong expression of cytokeratin 7.

Prognosis and predictive factors
The prognosis is generally good, although recurrences and local spread have been reported. Criteria for malignancy of pleural tumours include necrosis and a mitotic count of greater than 4 per 10 high powered fields, but the applicability of these criteria to tumours in the heart and pericardium is unknown.

Malignant mesothelioma

Definition
Malignant mesothelioma arises from mesothelial cells or demonstrates mesothelial differentiation. The definition of primary pericardial mesothelioma stipulates that there is no tumour present outside the pericardium, with the exception of lymph node metastases.

ICD-O code 9050/3

Epidemiology
Mesothelioma of the pericardium represents approximately 0.7% of malignant mesotheliomas {831}. As with mesotheliomas in other sites, the incidence may be increasing, due to the latency between asbestos exposure and tumour development {1074}.

Etiology
Like pleural mesotheliomas, a large proportion of mesotheliomas of the pericardium are induced by asbestos {1074}. Iatrogenically induced pericardial mesotheliomas have been reported decades after exposure to pericardial dusting with asbestos and fibreglass as a treatment for angina pectoris. Therapeutic radiation for breast cancer and mediastinal lymphoma has also been implicated in rare patients. However, there remains a subset of patients with mesothelioma who have no known exposure history.

Clinical features
Signs and symptoms
The mean age of patients with pericardial mesothelioma is about 45 years, with a wide age range, including elderly, older children and young adults. The initial course is usually related to pericardial effusions. Tamponade may eventually occur {1202}.

Imaging
Echocardiography usually shows pericardial effusions and may show pericardial thickening. However, because pericardium is at the periphery of the field of view obtainable with echocardiography, MRI or CT are usually necessary. MRI and CT usually demonstrate pericardial fluid as well as pericardial thickening and/or pericardial masses {737}.

Macroscopy
Malignant mesotheliomas of the pericardium can form bulky nodules that fill the pericardial cavity. The tumour can also spread diffusely over the pericardial surface and completely encase the heart. They can further encircle the great vessels and may obstruct the venae cavae.

Histopathology
Malignant mesotheliomas of the pericardium resemble pleural mesotheliomas. Although the majority are of the epithelioid type, forming tubules, papillary structures, and cords of infiltrating cells that can incite a desmoplastic response, the sarcomatous variant is also common. Variants similar to those described in the pleura may also be seen in the pericardium e.g. microcystic, adenomatoid, deciduoid {1649,1802}.

Immunoprofile
The immunohistochemical profile of pericardial mesothelioma is similar to that of pleural mesothelioma. Expression of mesothelial antigens, such as calretinin, and cytokeratins 5/6 are helpful in the diagnosis, as are negative reactions for adenocarcinoma markers, such as carcinoembryonic antigen.

Electron microscopy
Ultrastructurally, mesothelioma cells from epithelioid areas contain branched, bushy microvilli. Cytoplasmic tonofibrils are present in approximately 50% of tumours. Asbestos bodies may be identified within pericardial mesothelioma, but are of no diagnostic utility.

Differential diagnosis
The distinction between mesothelioma and pleural-based lung adenocarcinoma can be quite difficult, and is generally based on immunohistochemical findings. Distinction from reactive mesothelial cell proliferations may also be difficult; in comparison to reactive pleural mesothelial proliferations, reactive pericardial mesothelial cells may be more deeply "invasive". Reactive stromal cells may also often attain bizarre and pleomorphic shapes, confusing the histopathologic picture. Other malignancies that may be confused with mesothelioma include pericardial-based angiosarcoma, which may elicit a prominent mesothelial response, malignant solitary fibrous tumour and synovial sarcoma. Immunohistochemistry is invaluable in such circumstances. Mesothelioma lacks the X;18 translocation of synovial sarcoma.

Prognosis and predictive factors
The prognosis of pericardial mesothelioma is poor. Fifty per cent of patients

Exhibit G

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Malignant Pericardial Mesotheliomas and Asbestos Exposure: A Case Report

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Three cases of malignant pericardial mesotheliomas are presented with evidence of occupational asbestos exposure. Examination results are compared with findings from experimental and epidemiological research on biological effects of asbestos dust. There are sufficient indications that time-limited effects of asbestos dust established either by measurements or assessment of the amount of concentration after a latency of more than 20 years are apt to result in the development of mesotheliomas of the pleura and peritoneum and, moreover, the pericardium. It is suggested that malignant pericardial mesothelioma also be recognized as another form of occupational disease caused by asbestos dust.

Key words: asbestos, mesothelioma, pericardium, occupational disease

INTRODUCTION

Mesotheliomas number among the class of rare tumors. In the literature the annual incidences for mesotheliomas are given as ranging from one to less than three cases out of 1 million people, with diagnostic variations and the existence and mode of operation of regional or national cancer registers exerting an essential influence on the figures [Lemesch et al, 1976].

In the German Democratic Republic (GDR), a cancer register has been in existence for many years. Doctors in clinics, pathological institutes, out-patient departments, and medical practices are responsible for reporting any cancerous diseases and cases of death by cancer. Moreover, there is a regulation prescribing an autopsy in cases of death by cancer and in cases where there is a suspicion of cancer.

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In the course of the years from 1970 to 1978, 15 cases (in 13 men and 2 women) of malignant pericardial mesothelioma were registered in the National Cancer Register of the GDR.* Numerous publications have proved that, for mesotheliomas of the pleura and peritoneum, there is a connection between occupational and nonoccupatonal asbestos exposure (literature compilation by Bohlig and Otto [1975] and Selikoff [1979]). However, pericardial mesotheliomas have not been particularly mentioned in these reports. There are also only sparse indications in the medical literature concerning mesotheliomas of the epicardium and pericardium [Eck and Berg-Schlosser, 1978; Sytman and MacAlpin, 1971; Kahn et al, 1980; Roggli, 1981].

The purpose of this study was to check whether retrospective studies furnished proof of a correlation between malignant pericardial mesotheliomas and asbestos exposure. To this end, the 15 cases of pericardial mesotheliomas registered during the period from 1970 to 1978 were examined.

MATERIALS AND METHODS

For the retrospective study, all records concerning medical treatment, X-ray films, surgery reports, and autopsy findings were used. By interviewing relatives, we established the occupational anamnesis, including data concerning years and places of employment and kind of work done. The places of employment and jobs were checked in terms of industrial hygiene, establishing at the same time the kind of activity performed; materials, machines and tools used; emission and spreading of asbestos dust at the places of work; as well as data concerning duration and continuity of jobs involving exposure to asbestos dust. Interviews were conducted with workers, technologists, foremen, and engineers who had worked with the individuals examined or who had known the workplaces in the factory under examination for a long time.

For assessment of the housing and living conditions, we depended exclusively on information furnished by relatives. From this information, it was found that there was some indication of asbestos dust contact in four cases.

One case concerned a sailor who did service onboard a submarine for five years. A variety of reports on the use of asbestos as an insulating material at shipyards and other jobs known to involve the use of asbestos-containing packing material (asbestos cord, asbestos packings) for sealing pipe joints and fittings in ships suggest that personnel working within the range of the propelling machinery may be exposed to asbestos dust. Another man helped for several months to demolish a cold-storage unit, 25 years prior to the detection of a malignant pericardial mesothelioma. We found that, in the course of dismantling and repairing industrial plants equipped with numerous pipe conduits, short-term high asbestos dust concentrations will occur when insulations and packings contain asbestos.

When checking the jobs and workplaces of a young woman who died of a pericardial mesothelioma at the age of 33, it was found that for ten years she had worked in a room equipped with an electric heating installation that had a housing made of timber and asbestos slabs. The asbestos slabs served as fire guards. It was, however, no longer possible to check whether any asbestos fibers had loosened from those slabs. There

*The data were furnished by courtesy of the Central Institute of Cancer Research at the Academy of Sciences of the German Democratic Republic.

have already been indications in the literature about emissions of asbestos fibers originating from walls and ceilings in rooms built of asbestos material [Sawyer, 1977; Spurny et al, 1979].

Another case of pericardial mesothelioma was found in a man aged 46 who worked as a druggist for 30 years. In former times, it was common practice in a druggist's shop to store, weigh, and pack talcum or use it to prepare mixtures for body powder and wall paints. Druggists are thus liable to inhale asbestos fibers originating from asbestos-contaminated talcum.

There were no other explanations to back up these four cases. In five cases, there was never any contact with asbestos. In two cases, investigations are still going on. In the following, details will be given about three cases of pericardial mesothelioma taken from the 1970–1978 mesothelioma register where the retrospective study furnished proof of a job-related exposure to asbestos dust.

CASE HISTORIES

Case Number 1

This individual, aged 77, died in a clinic in September 1970. A few months before, an extension of the mediastinal shadow was detected on X-ray films. The diagnosis confirmed the existence of a malignant tumor. Because of the tumor's location and extension, an operation was no longer possible. Cachexia and anemia followed. Death occurred with a clinical picture of cardiocirculatory failure.

The autopsy showed a mesothelioma of the pericardium measuring $7 \times 6 \times 5$ cm with proliferation around the arcus aortae and vena cava superior. Metastases were found in the bifurcate, para-aortal-thoracic and cervical lymphatic nodes, spleen, right suprarenal gland, and intestinal serosa. There were no pleural plaques. Histologically, it was a mixed form of equal distribution of sarcomatous and carcinomatous elements. The histological slides were no longer available to be photographed.

The individual was employed as a mechanic in a big chemical plant from 1923 until 1957, working in a section where chlor gas was formed by electrolysis of alkali chlorides (sodium chloride). The electrolysis of the alkali chlorides was accomplished either in cells wth asbestos diaphragms or in mercury cathode cells. Both technological processes found large-scale application in this chemical plant, so that the mechanics were fully occupied repairing and servicing the electrolytic cells. This included the removal of the lids screwed onto the cells, the removal of the rest of the asbestos packing cord with the aid of sharp tools, and insertion of new asbestos cord. Diaphragm cells involved the additional removal and renewal of asbestos diaphragms. The gusset of the diaphragms was mechanically cleaned and coated with asbestos textile and a mixed mass of long-fiber asbestos. Workplace examination confirmed the emission of asbestos dust when the packing remnants were removed and new asbestos-containing packing cord was inserted and when the diaphragm gussets were cleaned and coated with asbestos. In past years no special protective measures (eg, respirators) were used because the danger involved in the emission of asbestos dust was not appreciated. On the other hand, in this chemical plant protective measures were observed for the prevention of diseases caused by the inhalation of mercury vapors at the electrolytic cells.

For more than 30 years, the man in question worked almost daily in the presence of short-term high concentrations of asbestos dust, inhaling asbestos dust into his lungs. The inhalation of asbestos dust and the spreading and penetration of extremely

fine asbestos fibers into the pericardium were regarded as the cause of the malignant pericardial mesothelioma, suggesting for the disease an occupational etiology. The medical opinion included the recommendation that a pension be awarded to the man's widow.

Case Number 2

A 63-year-old man suffered a pleural effusion in 1975 (Fig. 1). In the course of the examinations carried out in the lung clinic, no tumor or any inflammation was detected. In the following months, several pleural effusions were punctured and cytologically examined. No tumor cells were found. The man died seven months after the onset of the disease.

The autopsy disclosed a pericardial mesothelioma with diffuse growth between the inner and outer serous layers of the pericardium. In both the right and left pleural cavities, discrete metastasizing cancer cells were found invading the visceral pleura, and an inflammatory exudate was observed. Histologically, the tumor consisted of big, partly caudated cells, resulting in an overall adenoidal structure. There was no evidence of metastases to other tissues. The autopsy was carried out by a pathologist experienced in diagnosing mesotheliomas. No photos were taken.

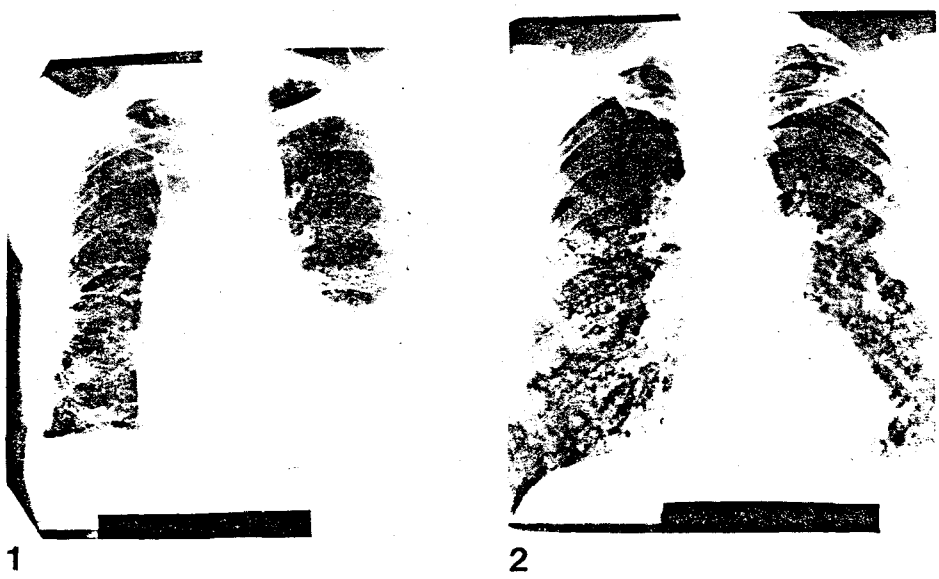
From 1939 to 1947 the individual worked for a total of 72 months as an engine operator in a factory producing lignite briquettes. He had to attend to the coal drying runners and the ring-roll press, to perform repair and maintenance jobs, and to help dismantle old plants. The foremen and engineers of that factory were able to give exact data on the workplace and the materials used. The ground lignite was dried in special driers (drying runners) by means of steam and hot air and passed on via conveyor equipment to the ring-roll press.

The various sections of the drying runners were bolted together and sealed with asbestos cord. For repair and maintenance of the drying runners, remnants of the packings had to be removed with the aid of sharp tools and replaced by asbestos cord; this involved short-term high concentrations of asbestos dust. When plants were dismantled, the asbestos insulations were also removed from the piping. The workers did not use respirators. Over the course of many years, the man in this case would repeatedly have inhaled short-term high concentrations of asbestos fiber dust. The asbestos dust effect was regarded as the cause of the malignant pericardial mesothelioma. This case was recognized as an occupational disease; the widow has been granted a pension.

Case Number 3

The X-ray films taken of the 48-year-old individual a few months prior to his death revealed a large round shadow and numerous small round shadows in his lungs; these shadows were viewed as a central bronchial carcinoma (Fig. 2). Moreover, the man was known to suffer from silicosis for several years. An operation was not possible.

The autopsy revealed, macroscopically, a 7-cm long and 5-cm wide cylindrical tumor of the epicardium in the region of the rear wall of the left ventricle. The invasive pericardial effusion of 1,050 ml was the result of a fine-tubercular-to-diffuse tumor diffusion into the pericardium and neighboring myocardium. Metastases were found in the intrathoracic lymph nodes, in the lung tissue, and in both kidneys. In addition, the individual had silicosis. While there were not pleural plaques, stringlike intergrowths of the pleural blades on both sides were found.



1 2

Fig. 1. Postero-anterior chest X-ray photograph (case 2). The mediastinum is expanded, and there is a reactive pleural effusion.

Fig. 2. Postero-anterior chest X-ray photograph (case 3). The picture shows in both lungs a great number of silicotic nodules and rather large round shadows of metastases.

Microscopically, the epicardial mesothelioma was rich in cells and revealed mostly epithelial and partly adenomatous elements, which covered the mesothelial bounds with tubercular overgrowth (Fig. 3). The medium-sized, highly polymorphous, partly triangular, caudated cells with drastically enlarged reticular nodes sat loosely on delicate connective tissue septa and surrounded fissurelike cavities appearing in outlines (Fig. 4). Some sections revealed an extensive infiltrating and destructive growth penetrating into the neighboring myocardial layers (Fig. 5). In the lungs, silicosis and the lymphogenic tumor metastasis were found.

In both the interstices and the alveoli, relatively small asbestos needles were found under the light microscope (Fig. 6). Multinodal giant cells were observed in tumor sections and also in the alveoli.

In his earlier years, the individual had worked in ore mines for 12 years and had inhaled quartz-containing mine dusts. He contracted silicosis as a result of his job in the mines. Later on, from 1958 to 1967, he was employed in a textile factory, working at a carding machine for treating sheep's wool. In a carding machine, the wool is passed over rolls and roughened up. When the wool is fed into the machine and passed through it, agglomerations form. For better movement of the wool, the machine minder dusts on talc powder by hand. After each shift the machines are cleaned and the wool remnants removed from the rollers and the driving gears by scouring them with compressed air and brushing them with little brooms. The application of talc powder and cleaning of the machines produce high concentrations of talc dust. We carried out numerous mineralogical tests with talc samples from various sources and found asbestos contents ranging from 2% to 5% and even higher in a few cases.

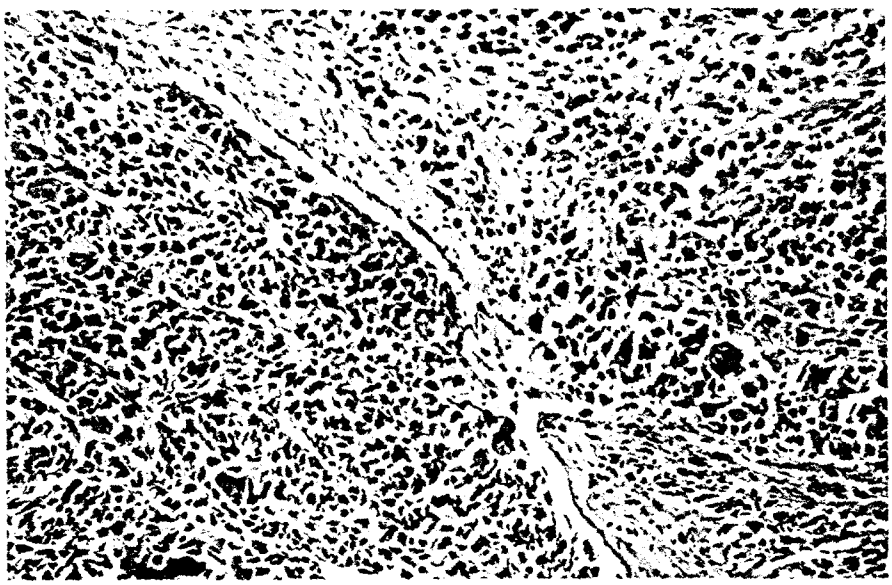


Fig. 3. Tumor with infiltration of the epicardium. The picture shows the mesothelial boundary in the middle. Hematoxylin-eosin ×160.

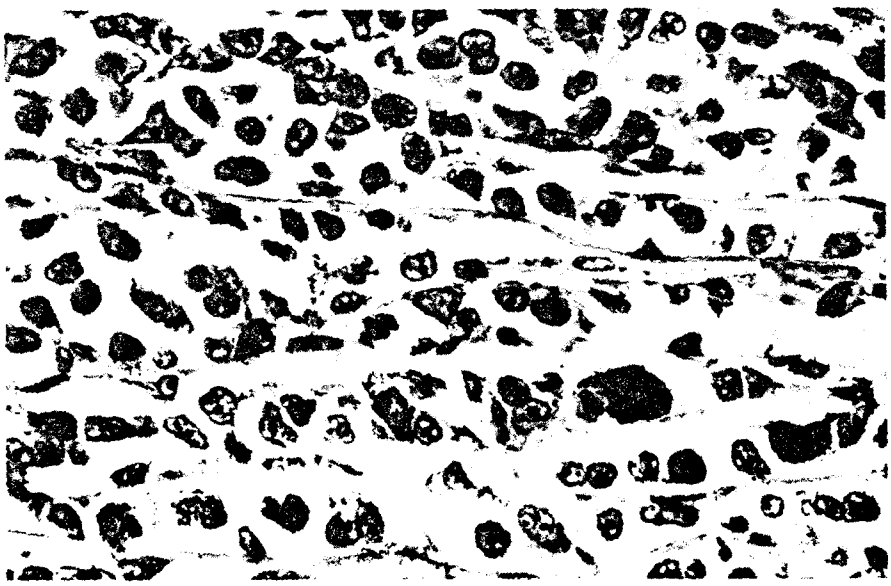


Fig. 4. Characteristic histological pattern of the mesothelioma with many triangular cells and prominent nuclei. Hematoxylin-eosin ×640.

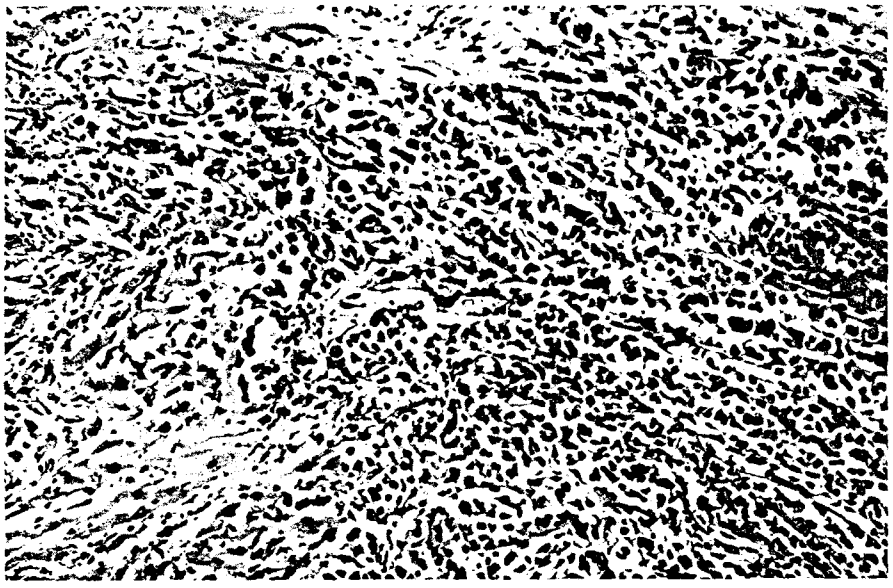


Fig. 5. Tumor with infiltration of the myocardium. Hematoxylin-eosin ×160.

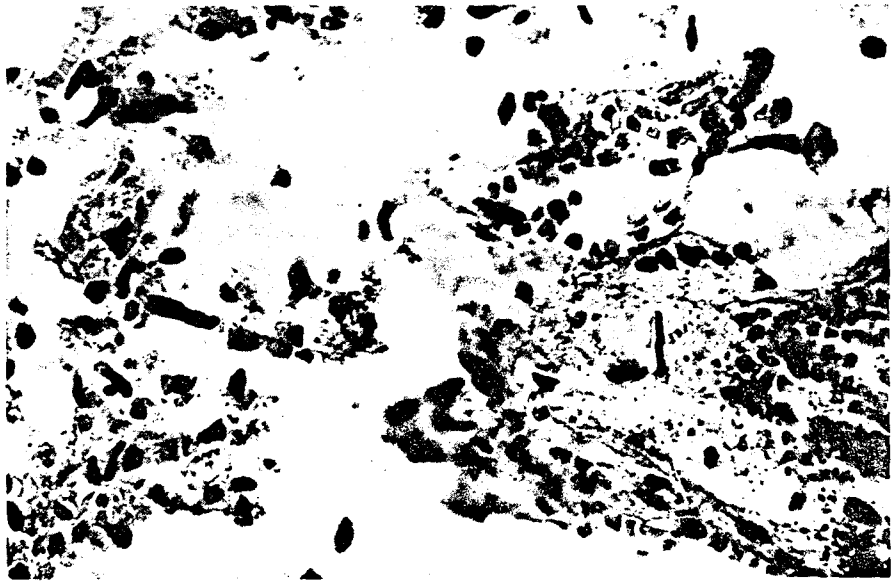


Fig. 6. Sections of the lung tissue with asbestos body fragments and dust. Hematoxylin-eosin ×640.

The use of talc powder on carding machines is an exposure source of asbestos fiber dusts. Because of the kind of work done by the individual in question, he was exposed every day to high concentrations of talc dust containing asbestos. Such exposures were considered to be sufficient for inhaling numerous asbestos fibers and were regarded as causative in the development of epicardial mesothelioma. This case was recognized as an occupational disease and the widow has been granted a pension. The silicosis as a secondary occupational disease did not result in a functional impairment of respiration, heart, and circulatory organs, and thus did not constitute the cause of death.

DISCUSSION

It is rare for malignant tumors to develop on serous membranes, in particular on the pericardium. Epidemiology has confirmed that mesotheliomas of the pleura and peritoneum are more frequent in individuals who work with or are otherwise exposed to asbestos dusts or materials containing asbestos. In the GDR, too, a close connection between asbestos exposure and malignant mesothelioma has been established. These mesothelioma cases, however, have involved mostly the pleura and peritoneum [Anspach, 1974; Beck and Irmscher, 1979; Bittersohl, 1975; Sturm, 1974].

Often the asbestos exposures mentioned in the examination reports are of short duration, covering only a few weeks or months, and do not even occur every day [Zielhuis et al, 1975]. Mention is also made of the effect of low asbestos dust concentrations [Goff and Gaensler, 1972; Irmscher et al, 1979; Murphy et al, 1971; Wei-Jen-Chen and Moffet, 1978]. Observations of mesotheliomas in women workers who produced gas masks are impressive examples of the danger involved in short-time asbestos exposures [Jones et al, 1976; McDonald and McDonald, 1978].

Carcinogenicity of asbestos has been established experimentally in the development of mesotheliomas [Reeves et al, 1974; Wagner and Berry, 1969]. Recently, experimental results on the cancerogenic effect of fine fibers, not asbestos, were reported [Pott, 1976; Pott et al, 1976]. Thus, there is a suspicion that not only asbestos fibers but also other mineral fibers are dangerous and apt to cause mesotheliomas [Stanton, 1974]; until now this assumption has not been tested. As for the question of whether pericardial mesotheliomas are also apt to originate in individuals exposed to asbestos, Kahn et al [1980] and Roggli [1981] have recently published case reports. Kahn et al found a mesothelioma in the pericardial cavity and observed asbestos particles in lung tissue under the light microscope. Following inspection with a transmission electron microscope, the fibers in the lungs were identified as amphibole asbestos (amosite). There were also other morphologic indications of exposure to asbestos such as pleural plaques and pleural fibroses. No examination of the tumor tissue was carried out to identify asbestos fibers. The case report is an impressive confirmation of the close connection between pericardial mesotheliomas and exposure to asbestos. The exposure was confirmed by the case history of the patient, who was exposed to asbestos at a shipyard 30 years before.

In three cases (1, 2, and 3) out of 15 involving malignant mesotheliomas of the pericardium and epicardium registered in the GDR during the period from 1970 to 1978, our retrospective studies have established with certainty the influence of occupational asbestos dusts. Following the information on occupational histories, asbestos dust exposures were probable in four more cases. This confirms our previous results of

epidemiological pleural and peritoneal mesothelioma examinations, which also established a high percentage of exposures to asbestos dust for the affected individuals [Beck and Irmscher, 1979; Sturm, 1974]. We were not able to carry out additional studies with the transmission electron microscope to identify asbestos fibers in the lungs and in the mesothelioma.

In the new List of Occupational Diseases in the GDR, which was passed into law in April 1981, "Malignant Tumors Caused by Asbestos" have been entered in the list as number 93. Given medical confirmation of a case of bronchial cancer, pleural mesothelioma, peritoneal mesothelioma, pericardial mesothelioma, and laryngeal carcinoma due to asbestos dust action, this list number serves as a basis for the recognition of these cancers as occupational diseases and the payment of social insurance benefits (pensions, equalization payments in case of loss of earning, sick pay, etc). Before this, following the old list, it was not possible to assign a number to peritoneal and pericardial mesotheliomas. In case of such mesotheliomas, the Chief Advisory Commission for Occupational Diseases at the Central Institute of Occupational Medicine in the GDR was required until April 1981 to recommend that such mesotheliomas be recognized as an occupational disease by special decision.

Medical appraisal of pericardial mesotheliomas is based on preliminary criteria for recognition of cancer as an occupational disease [Konetzke, 1973]. For a pericardial mesothelioma to be recognized as an occupational disease, both histological confirmation of the mesothelioma by pathological-anatomical examinations of the tissue and evidence that the individual in question inhaled asbestos dust in the course of his occupational activities are required. This calls for precise data on the type and duration of work, frequency of use of asbestos or asbestos-containing materials, and means employed in work (machinery, tools). A one-time asbestos exposure lasting a few hours only does not, in our opinion, qualify recognition of a pericardial mesothelioma as an occupational disease. Asbestos exposures that occur for a short time only during a work-shift but that recur in the course of several weeks, months, or years imply without doubt the inhalation of a large number of asbestos fibers into the lungs and may, thus, be the cause of mesotheliomas or bronchial cancer. Moreover, the action of asbestos dust depends on concentration, dispersion of dust particles, and asbestos content in suspended dust. Valuable information on dust measurements and mineralogical analyses available from earlier years will certainly be rare.

Nevertheless, dust development can be realistically estimated by precise surveys of all factors of influence at the former workplaces and by making comparisons with workplaces where similar technological conditions exist and where dust measurements have been carried out.

In cases 1 and 2 of this report, repetitive exposure to asbestos dust had been established, with asbestos dust concentrations definitely higher than under present workplace conditions.

Case 3 involved exposure to talc. There have been numerous publications about the occurrence of asbestos contained in talc [Blejer and Arlon, 1973; Hildick-Smith, 1976; Kleinfeld et al, 1973; Luckewicz, 1975]. In the GDR, talc is considered among the group of asbestos-containing materials, unless there is evidence by a mineralogic phase analysis that no asbestos is present. In numerous talc samples we proved the existence of asbestos contents ranging from 2% to 5% and in a few cases even more. In case 3, no results of mineralogic analyses of talc samples were available from past years. The talc samples formerly used did, however, stem from the same countries of origin as the

samples where asbestos was found. Thus, also in the case at issue, the effect of asbestos-containing talc dust was confirmed.

Hence, all three cases presented were based on exposures that, both in terms of dust composition and intensity of action (duration, dust concentration, dispersion), were sufficient for the individuals in question to inhale a considerable number of minute asbestos fibers into their lung tissues.

Although prevention of asbestosis is aided by internationally accepted values concerning maximum admissible dust concentrations, the observation of which is also prescribed by law and strictly supervised in the GDR, this does not include a qualitative description of the exposure-related cancer risk, because no international concentration limits (threshold) have been set. Even scientists are in doubt about a threshold level for cancer and of the risk present above the zero value [Schramm and Teichmann, 1977].

Latency periods from the beginning of the first asbestos exposure in this study until identification of a pericardial mesothelioma were 57, 36, and 30 years. From the literature and from our own experience, such long latencies seem to be typical for asbestos workers affected by pleural and peritoneal mesotheliomas as well. It is our opinion, therefore, that pericardial mesotheliomas also strongly suggest some connection with exposure to asbestos.

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Exhibit H

JOURNAL OF MEDICAL CASE REPORTS

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Case report

Primary malignant pericardial mesothelioma - a rare cause of pericardial effusion and consecutive constrictive pericarditis: a case report

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Abstract

Introduction: Primary malignant pericardial mesothelioma is a very rare pericardial tumor of unknown etiology.

Case presentation: A 61-year-old Caucasian woman was admitted to our hospital complaining of exertional dyspnea due to a large pericardial effusion. Intrapericardial fluid volume declined after repeated pericardiocentesis, but the patient progressively developed a hemodynamically relevant pericardial constriction. Pericardiectomy revealed a pericardial mesothelioma. Subsequently, four cycles of chemotherapy (dosage according to recently published trials) were administered. The patient remained asymptomatic, and there was no recurrence of the tumor after three years.

Conclusion: Pericardial mesothelioma should be considered and managed appropriately in non-responders to pericardiocentesis, and in patients who develop constrictive pericarditis late in their clinical course.

EXHIBIT H

Introduction

Primary malignant pericardial mesothelioma is a very rare pericardial tumor of unknown etiology.

Case presentation

A 61-year-old Caucasian woman was admitted to our hospital complaining of exertional dyspnea (NYHA III) and chest pain. Transthoracic echocardiography demonstrated a large pericardial effusion. Pericardiocentesis revealed 1500 ml of an acellular, sterile pericardial effusion and symptoms were markedly relieved.

The patient was re-admitted three months later, and transthoracic echocardiography showed a recurrent large pericardial effusion with partly organized fibrinous structures inside the effusion. There were no signs of cardiac tamponade, but there was a thickened right ventricular pericardium (Figure 1, Movies 1 and 2). Magnetic resonance imaging (MRI) confirmed the pericardial effusion, and the slightly thickened pericardium (Figure 2, Movies 3 and 4).

An F-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scan demonstrated an intrapericardial accumulation of the tracer, indicating a local infection or a tumor (Figure 3) [1].

The patient's level of intrapericardial fluid declined after repeated pericardiocentesis, and cytology of the pericardial fluid revealed signs of chronic infection, but no malignant mesothelial cells. Subsequently, the patient developed a hemodynamically relevant pericardial constriction (Movie 5). Therefore, a partial pericardiectomy was performed, and histological examination (Figures 4a and 4b)

Figure 1. Transthoracic echocardiography (apical 4-chamber view) demonstrating a large pericardial effusion and a thickened pericardium of the free wall of the right ventricle (see Movies 1 and 2).

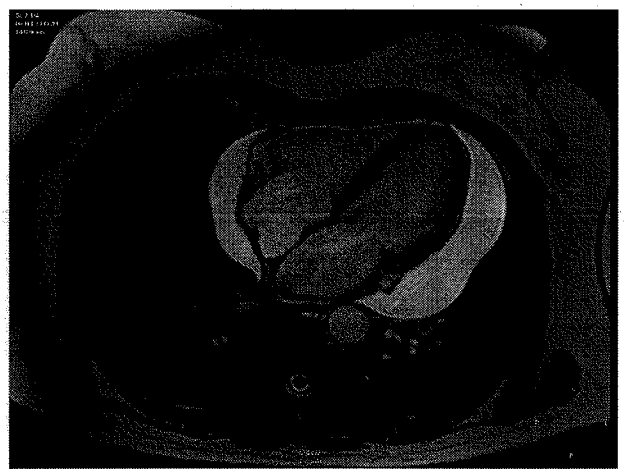

Figure 2. Magnetic resonance imaging (4-chamber view, turbo field echo [TFE]) confirmed the extended pericardial effusion without signs of cardiac tamponade, and a slightly thickened pericardium (see Movies 3 and 4).

revealed a primary malignant pericardial mesothelioma (PMPM). This finding initiated additional subtotal pericardiectomy with resection of as much pericardium as possible. The inspection of the epicardium by the surgeon showed a pericardial thickness of 10 mm and a white-colored spot of the pericardium at the right ventricle. There was no indication of tumor spread to adjacent structures, and there was no tumor on the epicardial site.

This was considered to be a PMPM because no signs of a pleural mesothelioma were found. Despite the above-mentioned findings of the magnetic resonance imaging (MRI) scan of the chest, FDG-PET, echocardiography and pericardiocentesis, we suspected PMPM but could not definitively declare a preoperative diagnosis of PMPM.

Subsequently, four cycles of chemotherapy with pemetrexed and cisplatin (four cycles in four months - dosage according to recently published trials) were administered, and remission was achieved [2-5]. The patient remained asymptomatic, and there was no recurrence of the tumor during the next three years.

Discussion

Diagnosis of pericardial diseases can be challenging and often requires a multimodal imaging approach including echocardiography, MRI, CT and FDG-PET scans [6,7]. The majority of reported pericardial tumors are metastatic in nature and indicate a poor prognosis. Primary tumors of the pericardium are extremely rare, and PMPM is a very rare pericardial tumor of unknown etiology [8-10]. So far, about 350 cases have been reported in the literature, and

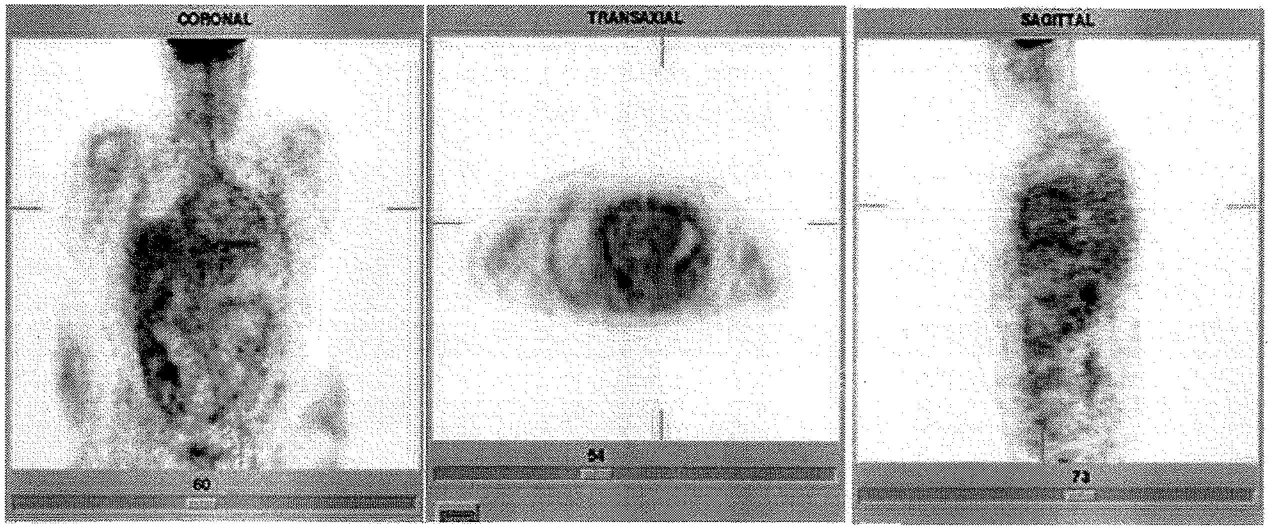

Figure 3. F-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scan demonstrating an intrapericardial accumulation of the tracer (Siemens ECAT HR+).

in an epidemiological survey, the annual incidence of PMPM was reported to be one in 40 million (incidence 0.0022%). PMPM is characterized by atypical solid growth of the mesothelium with formation of atypical cavities surrounded by fibrous stroma.

There is some recent evidence that asbestos may have a harmful effect on pericardial serosa. However, there has not yet been any definite proven association between asbestos exposure and pericardial disease [2,8-10]. Interestingly, our patient had a history of asbestos exposure at work (she worked in a school building).

PMPM is often discovered late during a patient's clinical course or at autopsy. Frequent clinical diagnoses refer mainly to acute pericarditis, constrictive pericarditis, and cardiac tamponade and sometimes to various types of coronary heart disease.

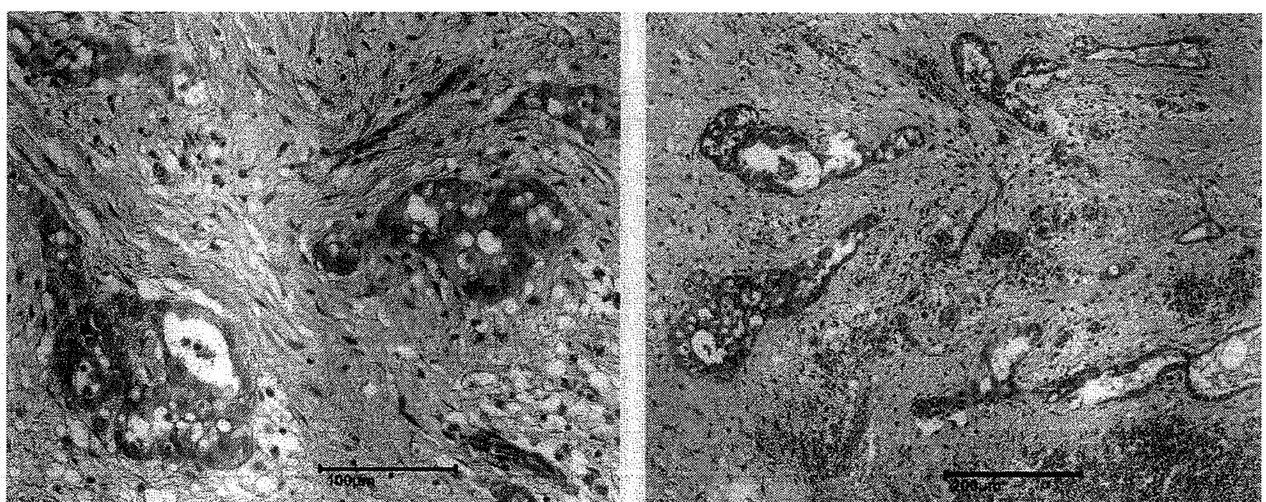

Figure 4a Figure 4b

Figure 4. Histological examination revealed diffuse infiltration of the pericardium by epithelioid cells due to the primary malignant pericardial mesothelioma (**a**: 100 µm, **b**: 200 µm).

Surgical resection remains the main treatment modality in PMPM. The prognosis of this disease remains extremely poor due to its late presentation, inability of complete tumor eradication by surgery and the poor response of PMPM to radiotherapy or chemotherapy. A median survival time from the onset of symptoms is six months [8-10]. Recently, newer chemotherapeutic regimens after complete excision of the tumor have shown prolonged survival times [2-5].

Conclusion
PMPM should be considered and managed appropriately in non-responders to pericardiocentesis or pericardial window for treatment of pericardial effusion or tamponade, and in patients who develop constrictive pericarditis late in their clinical course.

Abbreviations
CT, computer tomography; FDG, 2-fluoro-2-deoxy-D-glucose; FDG-PET, F-18 fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging; PMPM, primary malignant pericardial mesothelioma.

Consent
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
TB, LF, CL, AM, GP, HJT, DH and CP analyzed and interpreted the patient data regarding the cardiologic disease, therapy and the echocardiographic diagnostic. TB was a major contributor in writing the manuscript. JK analyzed and interpreted the magnetic resonance imaging; OL analyzed and interpreted the FDG-PET. AT and KMM performed the histological examination of the tumor. All authors read and approved the final manuscript.

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Supplementary Files
Movie 1. Transthoracic echocardiography demonstrated the recurrence of a large pericardial effusion and a thickened pericardium in the area of the right ventricle. Click on this link to play the movie (MP4): http://jmedicalcasereports.com/jmedicalcasereports/article/downloadSuppFile/9256/20505

Movie 2. Transthoracic echocardiography (subcostal view) demonstrating a pericardial effusion and a markedly thickened pericardium. Click on this link to play the movie (MP4): http://jmedicalcasereports.com/jmedicalcasereports/article/downloadSuppFile/9256/20506

Movie 3. Magnetic resonance imaging (MRI) confirmed the extended pericardial effusion without signs of cardiac tamponade, and a slightly thickened pericardium. Click on this link to play the movie (MP4): http://jmedicalcasereports.com/jmedicalcasereports/article/downloadSuppFile/9256/20507

Movie 4. Magnetic resonance imaging (MRI) confirmed the extended pericardial effusion without signs of cardiac tamponade, and a slightly thickened pericardium. Click on this link to play the movie (MP4): http://jmedicalcasereports.com/jmedicalcasereports/article/downloadSuppFile/9256/20508

Movie 5. Transthoracic echocardiography (subcostal view) demonstrating a markedly thickened pericardium and partly organised, fibrinous structures in the effusion. Click on this link to play the movie (MP4): http://jmedicalcasereports.com/jmedicalcasereports/article/downloadSuppFile/9256/20511